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BILIARY DYSKINESIA *

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THE trend of modern medicine toward the early diagnosis of disease has led to an increased interest in functional disturbances which may precede or even cause organic changes in structure.

In applying this viewpoint to the extrahepatic biliary passages, one may think theoretically of three kinds of functional disturbances, namely, of absorption, of secretion and of motility. Of these, we propose to discuss the disorders of motility or the so-called *biliary dyskinesia,* which may produce biliary stasis and the symptoms of gall-bladder distress or colic in the absence of calculus or inflammation. We shall give only a brief summary of the historical development, the physiologic basis and importance of this subject and point out certain pertinent observations we have made in our laboratory studies of the biliary tract.

Apparently the first clinical reports of gall-bladder colic without stone or infection were made by Krukenberg [1] in 1903 and Borghi [2] in 1913. These reports provided no explanation and attracted no attention. Undoubtedly many physicians have seen patients who have suffered gall-bladder distress without detectable anatomic cause and have explained the condition as being due to adhesions or to the passage of inspissated bile.

In 1909, the pathologists, Aschoff and Bacmeister [3] laid the foundation for further development of the concept of biliary dyskinesia by describing what they called the "stasis gall-bladder." They distinguished two kinds of "stasis gall-bladder," the hypertrophic and atrophic, in which either hypertrophy or atrophy of the wall, especially of the muscle layer, was found in the absence of inflammation or stone formation.

In 1920, Schmieden [4] in his important work on the "stasis gall-bladder" correlated the pathological with the clinical findings. He called attention particularly to those patients with typical gall-bladder distress in whom the surgeon at operation finds a markedly distended gall-bladder without calculus or inflammation. He thought that the distention of the gall-bladder was the cause of the distress, and that the distention was due to a mechanical

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hindrance to the flow of bile from the gall-bladder into the cystic duct. He thought the hindrance was due to an anatomical defect such as a kink, at the junction of the neck of the gall-bladder and the cystic duct (also see Rhode [5]). As is well known, this work was at first accepted with enthusiasm and later subjected to criticism because the hypothetical anatomic hindrance could not always be found.

In the meantime John Berg, the Swedish surgeon, was working on the problem and in 1922 he [6] suggested that a functional disorder of the biliary passages might be the cause of biliary stasis. This suggestion was supported by his observation of an accompanying hypertrophy of the muscle surrounding the ampulla of Vater. This hypertrophy has also been observed by Westphal,[13, 14] Nuboer [7] and Newman.[8] Giordano and Mann [9] have also found hypertrophy of the common duct sphincter in some cases of cholecystitis and peptic ulcer. Nuboer [7] has reported that the sphincter muscle is found to be hypertrophied in dogs 16 months after cholecystectomy and Westphal [14] has made a similar observation. Before this, however, Oddi,[10] in his classical work, and Meltzer [11] (1917) on the basis of physiologic theory had suggested that spasm of the sphincter of the ampulla may be the cause in some patients of biliary colic or icterus (also see Lyon [12]).

The concept of a "functional" cause of gall-bladder stasis has been especially developed and emphasized by Westphal,[13, 14] who, as a result of his experimental and clinical observations, classified and gave a general clinical description of the different types of biliary dyskinesia, their diagnosis and treatment.

Because Westphal's [13] experimental work on the guinea pig and rabbit led him to produce the first clear-cut classification of biliary dyskinesia, we shall briefly give an account of his observations. It should be pointed out, however, that his observations have not been fully confirmed. (For a review of literature, see Ivy [15]). Westphal regards the sphincter of Oddi as being composed of two parts, possessing a different structure and function. The first part consists of a proximal muscular coat which surrounds the antrum beginning at the junction of the duct with the ampulla. The second part consists of a distal group of muscle fibers which surround the papilla. The work of Lueth,[16] which the senior author observed, indicates that this view is probably correct. Westphal reports that when the vagus nerve is stimulated below the diaphragm with a weak current, the gall-bladder contracts, the antral portion of the sphincter manifests peristaltic movements and the papilla relaxes. He views this as being the normal type of response. With a stronger current, he reports that the tone of the gall-bladder is increased, and the movements of the ampulla are very lively. He suggests that this would cause a very rapid emptying of the gall-bladder, which, when it occurs in the human, he calls "hypermotile dyskinesia." When the vagus is stimulated with a still stronger current, he reports that the antral sphincter is thrown into spasm along with the contraction of the gall-bladder. This, he interprets, would cause spastic distention with pain, a condition he calls

"hypertonic dyskinesia." The difference between hypermotile and hypertonic dyskinesia is only one of degree of hypertonicity, and both are grouped under the general heading of "hyperkinetic dyskinesia."

On the other hand, when the splanchnic nerve is stimulated, Westphal reports that the gall-bladder and antral portion of the sphincter relax while the sphincter of the papilla contracts. This, he believes, would cause an atonic distention without much pain, a condition which he calls "atonic dyskinesia."

WESTPHAL'S CLASSIFICATION OF BILIARY DYSKINESIA

I. Hyperkinetic:
   a. Hypermotile. Increased motility of gall-bladder and ampulla with rapid emptying.
   b. Hypertonic. Contraction of the gall-bladder against spasm of the sphincter with *spastic distention* and colicky pain.
II. Atonic: Relaxation or atony of the gall-bladder with spasm of the sphincter of the papilla causing *atonic distention* of the gall-bladder with mild, continuous, "heavy," aching sensation.

Lyon [17] has classified the motor dysfunction of the extrahepatic passages into two types, "spastic dysfunction" and "atonic dysfunction," and suggests that in the course of time a spastic sphincter may cause the gall-bladder to become atonic. Smithies [18] has referred to the condition as "physiologic block," and Schmieden [19] has used the term "cholepathia spastica." Newman [8] has used the terms "spastic distention" and "atonic distention," and cautions against the division of dyskinetic states into hard and fast entities. We agree with Newman's caution.

In regard to this concept, which maintains that biliary distress may result from a motor dysfunction of the extrahepatic passages, two pertinent questions present themselves for answer. First, can the sphincter of the common duct, or the choledocho-duodenal mechanism, contract with sufficient force to prevent evacuation of the contracting gall-bladder? And, second, is it possible for the resulting pressure to produce pain in non-inflamed biliary passages?

In answer to the first question, only evidence obtained from lower animals is available. In the dog it is established that the gall-bladder may contract with a maximum force of about 30 cm. of bile pressure, which is also about the secretory pressure of bile; whereas the common duct sphincter, or the choledocho-duodenal mechanism, may contract and exert a resistance of as much as 80 cm. of bile pressure.[15] Thus, it is evident in the dog that a spastic choledocho-duodenal sphincteric mechanism may cause an intra-biliary passage pressure sufficient to block the flow of bile either from the gall-bladder or liver.

In answer to the second question, experimental evidence obtained from normal human subjects by utilizing two different methods for gall-bladder excitation is available.

First, by pilocarpine, a parasympathetic excitant: Westphal [14] passed a duodenal tube and initiated gall-bladder evacuation with olive oil. He then injected a relatively large dose of pilocarpine, a drug which in the dog causes gall-bladder contraction with some filling of the cystic duct but no evacuation due to contraction of the common duct sphincter. After the pilocarpine injection, he observed that the flow of bile into the duodenum ceased, following which gall-bladder distress was frequently obtained. This distress was promptly relieved by atropine which abolishes the action of pilocarpine on the gall-bladder and sphincter.

Second, by cholecystokinin, a hormone agency which acts chiefly by direct action on the musculature of the gall-bladder: During the past year, the senior author with Voegtlin and Greengard [20] has been studying the effect of secretin-cholecystokinin injections on the duodenal secretions in normal human subjects. The plan of the procedure is briefly as follows: The duodenal tube is passed. A number of control samples are obtained. Then a solution containing secretin and a little cholecystokinin is injected intravenously to determine the effect on the volume and chemistry of the duodenal contents. This injection generally produces a copious flow of both pancreatic juice and bile. In one of the first subjects, the following observations were made: After passage of the tube into the duodenum, a flow of bile-stained fluid was first obtained. Then the flow of bile-stained fluid ceased. Apparently a contraction of the common duct sphincter had resulted, shutting off the flow of bile. No distress was experienced at this time. Then the secretin-cholecystokinin solution was injected. A copious flow of pancreatic juice resulted which was not stained with bile. About 10 minutes later, right hypochondrial distress was experienced which gradually became more severe and finally was felt beneath the right scapula. After about 50 minutes, the distress was so severe that relief was sought. It was decided to ascertain if relief might be obtained by the introduction of magnesium sulphate. This was done and a few minutes after the introduction of the magnesium sulphate into the duodenum, the distress subsided and after seven minutes, dark bile was obtained from the tube. Cholecystographic evidence on this subject proved that the gall-bladder concentrated and evacuated normally. The duodenum and stomach were normal. Out of 19 normal subjects studied to date, biliary tract distress has been observed in three under these experimental conditions. This, we believe, constitutes a striking confirmation of Meltzer's [11] hypothesis that magnesium sulphate placed in the duodenum may relax the abnormally contracted sphincter of the common bile duct.

Until these observations were made, we were skeptical concerning the claim that pain can be produced in the non-inflamed biliary passages by such relatively low pressures as may be produced by the contraction of the gall-bladder. We were skeptical in this regard because Schrager and Ivy [43] had found in the dog that the minimal pressure required to elicit pain by distending the gall-bladder was 54 cm. of water, and by distending the bile

ducts 27 cm. of water. However, it is to be noted that the pressure required to elicit pain from the bile ducts in the dog is just about the secretory pressure of bile and the maximum force of gall-bladder contraction. Also, Ivy and Oldberg [21] observed pain distress with nausea and vomiting in a dog with the cystic duct occluded following the injection of cholecystokinin. Von Bergmann [22] has observed that the injection of dehydrocholic acid, which stimulates the formation of bile, into patients with common duct stenosis causes pain. This evidence and our observations on man cited above have convinced us that pain may be elicited from non-inflamed biliary passages by the maximum pressure that may occur in their lumen, provided the pressure is raised rather rapidly, especially in the presence of a tonic musculature.

According to the German school, biliary dyskinesia is due to an abnormal parasympathetic or sympathetic innervation. Newman [8] and Lyon [17] are inclined to the view that there are constitutional factors which predispose to either of the two types of dyskinesia. Boyden [23] describes three types of responses of the normal human gall-bladder to stimuli, which appear to depend primarily on how the sphincter responds, but has not attempted to relate these types to predisposition to dyskinesia.

In regard to the etiology of this condition, we believe that one must not neglect to consider the duodenum, the tone and motility of which is closely related to the functioning of the common duct sphincter.[16, 24] For example, Crain and Walsh [25] have demonstrated that experimentally induced duodenitis delays evacuation of the gall-bladder; and Shapiro and Kasabach [26] have found that a partial duodenal obstruction may also delay gall-bladder evacuation.

Most students of the subject of biliary dyskinesia, as we have indicated above, would place the cause of the functional obstruction solely at the site of the common duct sphincter. However, another possible site should be considered, because it is possible that a sphincter may be located at the junction of the neck of the gall-bladder with the cystic duct. Whether such a sphincter, which has been called the "collum-cysticus sphincter," exists anatomically, is disputed.[15] Lütkens [27] from Aschoff's laboratory, reports that he was able to find such a sphincter in 75 per cent of human subjects. Certain physiologic evidence submitted by Volborth [28] and Potter and Mann [29] suggests the existence of such a sphincter. Westphal [14] claims that such a sphincter is present in dogs and derives its motor innervation from the vagus. Careful cholecystographic study in man should in the course of time provide an answer; because, if the "collum-cysticus" sphincter is spastic, the gall-bladder when excited should manifest annular bands of contraction without the expulsion of contents resulting. Whereas, if the common duct sphincter is spastic, the gall-bladder should expel contents and the hepatic ducts become visualized. Both have been reported to occur in dyskinesia patients.[30-33]

The concept of biliary dyskinesia, which we believe to be established, not only provides an explanation for the "stasis gall-bladder" of Aschoff,

but also provides a mechanism with which to visualize the cause of stasis which predisposes to infection and stone formation. When this is more widely appreciated and recognized, it is not unlikely that the incidence of cholelithiasis, particularly in pregnancy, may be reduced by appropriate prophylactic therapy. The literature on the relation of pregnancy to the evacuation of the gall-bladder is meager (Ivy [15]). Westphal [13, 14] and Kalk and Schöndube [32] made observations which led them to believe that a hyperkinetic dyskinesia was present in early pregnancy. (See also references 23 and 34–39.) But a large series of patients has not been studied. This obviously important topic needs investigation.

This concept also provides a rational basis for gall-stone colic without gall-stones, for so-called "cholecystitis" with a normal gall-bladder at operation, and for so-called "hepatic neuralgia." It is further possible that the presence of an irritable or hypertrophied sphincter of the common duct may explain the recurrence of symptoms in some patients following cholecystectomy. The early relief would be due to the temporary paralysis of the sphincter that always follows cholecystectomy. But, after recovery from the temporary paralysis, the irritable or hypertrophic sphincter may again produce symptoms of biliary tract distention. The recognition of this possibility should emphasize the importance of the medical rather than the surgical management of these patients, although it must be recognized that some dyskinesia patients are benefited by cholecystectomy and some patients with residua after cholecystectomy are benefited by choledochoduodenostomy. In this connection, Aschoff [42] reports a series of 215 cases in which 25 stone-free gall-bladders were removed; of the 25, seven had residual symptoms accountable for only by dyskinetic processes. (See also reference 40.) It is likely that the number of discouraging results may be fewer when the idea of a functional disturbance is better understood and managed therapeutically by the surgeon and internist.

As indicated in the introduction to this paper, we did not propose to discuss the diagnosis and treatment of biliary dyskinesia. (For discussion of diagnosis and treatment, the reader is referred to the following references: 8, 13, 14, 17, 19, 22, 30, 31, 32, 33, 40.) We should state, however, that we do not believe the diagnosis to be simple. The presence of pain in the gall-bladder region with a normal 14 hour cholecystogram and absence of clinical evidence of an inflammatory process may lead one to suspect but not diagnose a dyskinesia. In this paper we have desired only to emphasize that the possibility of the occurrence of biliary dyskinesia should be borne in mind and requires consideration in the etiologic analysis, diagnosis and therapy of biliary tract diseases.

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PROLIFERATIVE AND EXUDATIVE TUBERCULOSIS WITH REFERENCE TO THEIR RELATIONSHIP TO THE VARIOUS FRACTIONS DERIVED FROM THE TUBERCLE BACILLUS *

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Our conception of tuberculosis has been subject to vast changes since Villemin proved the transmissibility of the disease and Koch revealed the cause of infection.

The pathology of tuberculosis received a clarifying and purifying touch when the discovery of the bacillus showed the unity of all tuberculous processes; and again, when Koch showed that sensitization of tissue cells plays a part in every infection. When the meaning of these two important facts was comprehended we were ready to define the pathologic changes which take place at the site of infection as the reaction of the tissues to the presence of the tubercle bacillus and bacillary products; and to view the reaction of the tissues of previously infected individuals, on again coming in contact with bacilli or bacillary substances, as shown in the phenomena attending subsequent invasion and in the tuberculin tests, as being evidence of a specific defensive mechanism.

The primary reaction in first infection is similar to the reaction of tissues to any foreign substance; but this changes and takes on aspects of specific opposition to the invading living organism as soon as sufficient bacillary substance has gained access to the circulation to sensitize the body cells. Thereafter the more simple reaction of first infection assumes a greater complexity because the entire organism has become prepared in a specific way to meet reinfection and to cope with whatever injurious substances are produced as a result of the growth and destruction of invading bacilli.

The anatomic pathology of tuberculosis consists of the changes in the tissues which are produced when infecting bacilli or bacillary products come in contact with body cells sensitized by bacilli and their products. The clinical expression of tuberculosis consists not only of the changes which are caused by the pathologic structure itself but also of reflex and toxic effects which are expressed in various tissues and organs, disturbing their smooth working and causing departures from physiologic action. It is evident that these expressions may be either local or general.

The difference in reaction of different individuals to tuberculous infection has led to certain groupings of cases according to the predominant characteristics noted. If it were possible for us to know the particular

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factors which determine these major differences, we would thereby greatly increase our understanding of the disease.

Even Sydenham and Morton, clinicians of the seventeenth century, recognized an arbitrary classification of tuberculosis into "early," "moderately advanced," and "far advanced." This was based largely on symptomatology and on the recognition of the fact that those with few, mild symptoms were curable and those with serious symptoms were seriously ill and for the most part incurable.

Later a classification, using the same terms, was proposed by Turban, which with modifications, is still followed in many countries of the world. This classification at first depended on anatomical extent only, but later was modified in the United States by Rathbun's suggestion of adding to it the severity of symptoms, and later by Brown and Heise's suggestion of adding the knowledge gained by the roentgen-ray.

These classifications have rendered a great service to tuberculosis, mainly by requiring physicians to appreciate that the smaller the lesion, other things being equal, the more curable the patient; and further by stimulating physicians to develop skill in determining early lesions. They have, however, added little to our clinicopathologic conception of the disease.

A real understanding of tuberculosis and the ability to predict what course a given infection will take depends upon facts which are more fundamental; facts of an immunologic nature which, if they were known to us, would be sufficient to explain many of the mysteries which at the present time surround the disease.

The reaction between the tissues and the bacillus throughout the course of tuberculosis is a combination of cell proliferation and exudation with or without tissue destruction. The predominating reaction in different lesions has been used as a basis for classifying them into proliferative or fibroid, exudative and caseopneumonic. Miliary tuberculosis is usually classified separately, although it may be predominantly proliferative in one case and predominantly exudative in another.

While these reactions are not distinctive and separate, but go hand in hand in the same lesion, yet one or the other predominates sufficiently often to show that a different combination of forces is responsible for the different reactions. Anything that will enable us to explain these differences will clarify our knowledge and help us to understand better the specific protective mechanism which the body brings into play when it combats tuberculous infection. We must bear in mind that these reactions are a part of the patient's defensive immunity mechanism, or at least are determined by it.

What reaction will take place in the tissues in the presence of invading organisms is determined primarily by the tissues themselves and secondarily by the numbers and virulence of the invading organisms. That heredity is a factor of great importance is conceded, and that the reaction of the tissues is greatly modified by environment, both internal and external, is likewise recognized. On the part of the bacillus, we have two important factors—

numbers and virulence. These four factors are the most prominent forces so far as we know in determining the nature of a tuberculous infection.

If we now turn to the bacillus we find that, under the direction of the National Research Council, Anderson and his coworkers have separated it into several distinct fractions, and that the effects of these various components on the tissues have been studied experimentally by Sabin, Doane, Cunningham, Long, Seibert, and their coworkers, with the result that certain reactions in the tissues may be more or less accurately assigned to definite bacillary substances.

These are among the most important studies that have been made in tuberculosis in recent years, because they give us a basis for understanding the individual reactions of the body against the disease.

The following fundamental reactions have now been assigned to the different components of the bacillus by these workers. The lipoid portion of the bacillus is the cause of the formation of the tubercle. The phosphatide constituent seems to possess the simple property of stimulating monocytes and young connective tissue cells to the formation of epithelioid cells and giant cells. The waxes cause proliferation of fibroblasts; and the acetone soluble fat induces proliferation of all connective tissue cells and the cells of blood vessels, and is responsible for hemorrhage. The polysaccharide is toxic for leukocytes and according to White exerts a damaging influence on the adrenals. The protein is responsible for fever, causes proliferation of plasma cells, produces sensitization of the body cells and calls out the allergic reaction later.

The lipoids seem to have most to do with the building up of a structural defense while the proteins are more intimately connected with the physiologic protection of the body.

While our knowledge is not sufficiently advanced to enable us to discuss the various pathologic changes in their exact relationship to this experimental work, yet we undoubtedly can make certain comparisons which are helpful.

Since the two outstanding tissue reactions in tuberculosis are the proliferation of cells, on the one hand, and the exudative reaction of allergy on the other, and since the former has been more or less definitely assigned to the lipoids and the latter to the protein fractions of the bacillus, it might be well for us as clinicians to accustom ourselves to think in terms of these reactions. It would seem fair to assume that the lipoids protect the body by holding the bacilli fixed in the tissues; and there is also a possibility that these cells afford a certain protection to the bacilli which they imprison. The proteins interfere with the migration of bacilli by causing inflammation and exudation in the tissues which surround them, and if the numbers and virulence of the bacilli are great the reaction may be sufficient to destroy the tissue and eliminate the bacilli en masse. The reaction to the protein elements further opposes multiplication of bacilli by increasing phagocytosis

and stimulating other defensive mechanisms of the body which encompass their destruction more rapidly and more efficiently.

Now if we examine into the nature of preponderantly proliferative tuberculosis, we note first that it is comparatively mild, and its chief characteristic is new tissue formation. It may extend until wide areas of fibrous tissue are formed before it makes its presence felt by symptoms. It is usually brought to the patient's attention by metastases taking place in some other portion of the lung or in some other organ, or by the process taking upon itself exudative and not infrequently destructive characteristics.

The primary mildness is indicative of a relative absence of physiologic disturbance of the patient, and suggests an infection produced by few bacilli with relatively low virulence which fails to stimulate adequate specific defense. The infection fails to furnish sufficient bacillary protein or to pour toxins into the circulation in sufficient quantities to produce symptoms, and yet regardless of this mildness the tissues are unable to prevent the bacilli from spreading. We must assume, therefore, that there are other factors which require explanation. It would seem that some protection must be present to shield the bacilli from destruction, for they continue to spread regardless of their low numbers and low virulence; or it may be that some factor necessary to encompass their destruction is wanting.

In this connection it will be remembered that Sabin has suggested that the monocytes which are precursors of the epithelioid cells exert a protective influence on bacilli. So the bacilli may not be destroyed, even though they are few in number and low in virulence; consequently they may fail to set free in sufficient quantities the tuberculo-protein which is necessary to build up the patient's physiologic protective mechanism (immunity) to the point of efficiency, although they do set it free in sufficient quantity to sensitize the body cells.

Sooner or later, however, this structural protection, if we may so speak of it, fails; bacilli develop in larger numbers, and through their growth and destruction larger quantities of bacillary protein are liberated which now call forth allergic phenomena and cause the widespread, mild, proliferative lesion to take on exudative characteristics with or without destruction of tissue. When this occurs the allergic reaction may be coextensive with the unhealed lesion which is not infrequently coextensive with the proliferative process; but as a rule, for some time the exudative phenomena are less marked than those found in primarily preponderantly exudative lesions. This indicates that regardless of the minimal amount of bacillary protein which had escaped from the proliferative lesion, sufficient had gained access to the body cells to cause at first sensitization and later a certain amount of desensitization. The chief allergic reaction and the principal destructive phenomena are usually confined to limited areas; it may be a single area at first which may proceed to cavitation. Later, however, when the allergic process becomes more extensive and more severe, multiple small cavities often appear in the midst of the proliferative process.

The supervention of exudative phenomena on a proliferative background probably results whenever the numbers of extensions of the disease become so many at any one time, or whenever they are caused by so large a number of bacilli that local destruction of tissue results and the total amount of bacillary protein set free into the tissues becomes sufficiently great to produce widespread allergic reaction with or without increased tissue destruction. It would seem then that our best conception of preponderantly proliferative tuberculosis is that it is primarily more a reaction of the tissues to bacilli as foreign bodies than to them as living, multiplying microörganisms which stimulate the body functions to their own destruction; consequently an infection in which structural defense predominates over physiologic defense. Whether this is for the most part due to the cellular protection afforded to the bacilli by the newly formed tissue or to the fact of a failure to set free sufficient amounts of immunizing protein and whatever other substances are necessary to create an efficient immunity is not clear. That bacillary protein may be lacking in these lesions is suggested by the fact that if the course is progressive, the effects of large quantities of bacilli and bacillary protein sooner or later become evident, and the lesion takes on exudative characteristics similar to those of the preponderantly exudative type; and further by the fact that the proliferative lesion may be stimulated to allergic response and healing by bacillary protein as found in tuberculin.

While preponderantly proliferative tuberculosis is mild in degree and usually consistent with long life, it does not heal readily. It is much more difficult to secure a satisfactory recovery from it than it is from the more acute exudative lesions.

Preponderantly exudative tuberculosis, on the other hand, is more acute. Even the early implantations are often made by large numbers of bacilli and are accompanied by the liberation of large quantities of bacillary substances of which the protein fractions are particularly in evidence. Not infrequently the first intimation of illness is accompanied by acute symptoms of toxemia, rise of temperature, weakness, even prostration, and often cough and expectoration. Examination at this time may reveal a widespread exudation in the tissues, not infrequently with loss of tissue. Here, physiologic reaction predominates over structural defense.

The disease may develop slowly as a result of a succession of small implantations of bacilli, or it may come on acutely as a result of massive dosage. In this connection it must be borne in mind that the term "numbers of bacilli" is not a measured dosage but a relative term depending on the individual and his antecedent dosage; for desensitization takes place as a result of repeated inoculations. So what would be a large dose at the beginning of a disease would probably be small later in its course.

With this form of the disease the patient is more severely ill than with the preponderantly proliferative form. There is more danger of the disease spreading quickly and more danger of tissue destruction. On the other hand, a higher immunity develops. The acuteness of the symptoms is

probably caused largely by the protein fractions of the bacillus which produce a widespread exudation with or without tissue destruction, although destroyed tissue products and other bacillary elements can not be excluded. The same dose of bacilli or bacillary protein which causes the acute symptoms seems to whip up the immunizing mechanism and to desensitize the patient so that he is thereafter enabled to withstand the effects of larger numbers of bacilli and of greater quantities of bacillary protein without reacting so severely. While proliferation goes hand in hand with exudation and destruction, yet it is relatively a minor part of the early stage of preponderantly exudative lesions but a very important part of the healing process.

Preponderantly exudative lesions yield readily to treatment if it is applied at once. The infection is not coextensive with the exudative phenomena, but must be looked upon as being a limited infection with a large local tuberculin reaction which, when it has cleared away, which it will do largely by resolution, will leave a fairly free lung field. Being acute it comes on before the lung has been seriously injured and when its power to make necessary compensation for healing is unimpaired.

FURTHER STUDIES ON GRANULOPENIA WITH A REPORT OF TWELVE CASES *

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Synonyms

With the increasing incidence of this disease, it is natural that new terms should be used. The original name was agranulocytosis and the indices usually refer to it under this heading or as agranulocytic angina. Agranulocythemia and hypogranulocytosis are also used—the former as a synonym of agranulocytosis and the latter to mean a leukopenia but not a complete granulopenia. Malignant neutropenia and primary granulocytopenia are used in the same sense as agranulocytosis or complete granulopenia. Primary granulopenia is also used in the sense that the granulopenia does not result from any other disease. Two points need to be distinguished. Complete granulopenia or near complete granulopenia or agranulocytosis is a rare and dangerous disease of the bone marrow. Mild or moderate granulopenia is a very common state of the blood stream and not in itself very dangerous. Complete granulopenia is a disease, leukopenia a mild decrease in the leukocytes. If the terms be limited to the granulocytes, one may distinguish the two conditions as complete and incomplete granulopenia. Partial or total granulopenia are other qualifying adjectives meaning the same thing. We prefer the terms complete and incomplete granulopenia to distinguish the rare disease from the frequent state.

The Mechanism of Complete Granulopenia

To understand the mechanism of the disease is to understand the disease itself with, of course, certain limitations in our present knowledge. The order of events in this mechanism was submitted at length in our first paper [1] and we believe with reasonable evidence of proof. There are five stages of the disease and they follow each other with inevitable and inexorable regularity. First and for some reason, now largely speculative, there is the bone marrow onset. The bone marrow is an organ and its myelocytic function fails. So far as we can see, it makes little difference whether one speaks of this selective myelocytic failure with cessation of the production of the granulocytes as a myelocytic aplasia, myeloblastic dysfunction, cessation of maturation, allergy or what not. It is a selective bone marrow failure with a resultant blood stream granulopenia even to the point of a complete absence of the circulating granulocytes. Secondly, about four days after this bone marrow failure, there is the blood stream onset. The

* Read at the Chicago meeting of the American College of Physicians, April 19, 1934.

change may appear in the blood count in one to two days with gradual lessening of the granulocytes to complete or near complete absence. Thirdly, the clinical onset comes more quickly, usually in 24 to 48 hours with complete granulopenia, weakness, prostration, and fever; rarely early mania and later exhaustion and delirium. Fourthly, the granulocytes protect the tissues with an ever present daily immunity from bacterial invasion. This protection is now lost, and bacterial invasion begins. Therefore, so far as is now known, this is a non-bacterial disease with a bacterial ending. Blood stream infection, tissue necrosis and gangrene, ulceration and hemorrhage follow. This is the stage of sepsis. Fifthly, and lastly, the parting of the ways has come. It is granulocytes or death. There is no mid course. The bone marrow may even resume its myelocytic function, but death may occur from sepsis before maturation proceeds to the appearance of myelocytes and granulocytes in the blood stream. This is the mechanism of complete granulopenia. One may object that this is too mechanistic a conception for a hematological problem, but the facts square with the conception.

Relative Frequency of Mild Granulopenia and the Chronic Granulopenic Patient

In our second paper we [2] studied the general subject of granulopenia and made comments illustrating the granulopenic trend on the basis of blood studies on 8,000 private patients. The general conclusions have been confirmed by a similar study made by Mettier and Olsan [3] at the University of California Hospital on 10,000 cases between 1920 and 1931, inclusive. A study of our paper and their paper shows the frequency of leukopenia, its trends and its wide implications. In general it may be said that leukopenia is an important factor and probably as important as a leukocytosis.

The granulopenias are classified under 10 different headings of which acute complete granulopenia is only one. A chronic granulopenia is described of which acute granulopenia is probably an extreme degree. One out of every four patients may be expected to have a mild granulopenia. One of two female patients between the ages of 40 and 60 may be expected to show a mild granulopenia. The complaints of weakness, exhaustion and fatigue are twice as frequent in the granulopenic patients as in those with normal white cell counts. There appears to be a definite even if rather vague clinical syndrome that consists mainly of weakness, easy exhaustion and chronic fatigue, a loss of strength with physical inertia associated with a chronic diminution in the number of granulocytes. The severity of these symptoms which are, of course, largely subjective, seems to depend upon the degree of diminution of the granulocytes until with complete absence of the granulocytes such as characterizes an acute complete granulopenia, there is extreme weakness and physical collapse. Mettier and Olsan found 1,167 patients out of 10,000, or 11.67 per cent, with granulopenia. Their figures show 52.4 per cent in females and 47.6 per cent in males. They classified 9.7 per cent of their cases of leukopenia as "benign leukopenia of obscure

origin." The careful and prolonged study of a single leukopenic patient rather than the mass study of many leukopenic patients promises valuable results.

Granulopenia whether acute, chronic or recurrent, is regarded as a disease entity in the same sense and as definitely as pernicious anemia is so regarded. Granulopenia, when associated with other diseases (usually then called leukopenia) is not rare, and here Fitz-Hugh and Comroe [20] well call it "a mere hematological manifestation" of other diseases. Among these may be mentioned typhus and typhoid fever, influenza, measles, mumps, dengue fever, certain stages of tuberculosis and syphilis, fulminant sepsis and later stages of extreme anemias. It is a common and widespread hematological condition long known and often used as a diagnostic aid. A college student with 80 per cent lymphocytes in a total leukocyte count of 1,600 was treated for the disease acute granulopenia, but developed on the fourth day definite signs of typhus fever; and an old man of 77 with only 34 per cent granulocytes in a total count of 2,000 was proved to have an advanced hypochromic anemia. A leukopenia with complete or near complete absence of the granulocytes, which constitutes the essence of the disease granulopenia or agranulocytosis, is one thing, and a leukopenia that is a blood sign of a disease of which it is a part, is quite another thing. Fine judgment and acumen may be necessary to make the differentiation. Sometimes only waiting will solve the problem. The point to be emphasized is that a low granulocyte count is not of itself proof of the disease granulopenia.

Granulopenia occurs in aplastic anemia. Here all three of the elements in the bone marrow are affected, viz., the granulocytic, the erythrocytic and the thrombocytic cells. In the disease granulopenia only the myeloblastic tissues are involved. Wide variations and gradation occur in the count of the granulocytes in pernicious, aplastic, and hypochromic anemias, and even in the aleukemic states of the various leukemias and particularly the myeloid type. In the last great care is necessary, for a leukemic patient may present a leukocyte count of 2,000 or less. The majority of these cells may be the blast type of the myeloid series. It is easy on account of their relatively small size to call them lymphocytes in error and make the diagnosis of granulopenia. At times a myeloid leukemia is so closely imitated by the leukopenia of other diseases, including certain anemias, that one must take all precautions to be sure of the diagnosis. Complete granulopenia seems to characterize agranulocytosis alone. It is the case of incomplete granulopenia that brings the greater difficulty. Of course the clinical signs and symptoms are of great aid.

The World Incidence and Geographic Distribution of Complete Granulopenia

Our present knowledge of the world distribution of granulopenia is dependent upon reports in the literature. The diagnosis of the disease depends upon the study of the blood, and in those areas and countries where

blood studies are the exception rather than the rule, the disease may occur as frequently as in America or Germany and yet be overlooked. Even in America it is reported far more frequently as a rule in those centers where a certain group are particularly interested in the disease, its problems and treatment. Blood studies are requisite for its recognition. There seems no available reason why it should not appear as frequently in England as in other civilized countries and the failure to make systematic blood counts is probably the reason for the paucity of English reports. From the literature to date (and more cases are reported from month to month) there is evidence that it is of world-wide distribution. The facilities for blood studies and for reporting disease are probably more highly developed in Germany and the United States than in other countries, and these two countries so far furnish the majority of reported cases. We have summarized 473 cases in the United States and over 400 in Germany. Reports continue to come in from France and Italy. It has been reported from Japan, China, Dutch East Indies, Russia, Poland, and Syria. Dennis [4] writes that cases have been seen in Palestine and Egypt, and several cases have been studied by Dr. Kleeberg in Jerusalem. So far only six cases are reported from England. Time will finally show its real incidence and distribution.

Age, Race, Sex, Occupation and Social Incidence

Acute granulopenia may occur at any age from less than a year to more than 80 years of age. The majority of cases occur between 30 and 50 and the average age of the 473 cases reported in the United States is between 40 and 50 years. It is chiefly a disease of middle life so far as reported cases show. This age incidence is an urge to complete and even repeated blood studies in cases of doubtful diagnosis.

So far the disease affects principally the white race. Its frequency in the yellow races is unknown. Further reports are necessary to clear this point. We have not observed a single case in the negro over a period of five years and with an annual admission rate of 75,000 negroes to the Emory University Division of the Atlanta City Hospital. This rarity in negroes seems to be true throughout the continental United States. Further facts are necessary before its final incidence in negroes can be stated. Sick negroes outside hospitals rarely have blood counts and most sick negroes never enter a hospital. In the eight cases listed below in negroes, the clinical onset in nearly all of them followed the administration of arsphenamine. The following table gives the present trend of race and sex incidence:

Table I

Number of cases in the U. S.	473
Number of cases in the white race	442
Number of cases in the colored race	8
Race not stated	23
Number of cases in males	161
Number of cases in females	310
Sex not stated	2

Thus far the disease is reported in the ratio of nearly two females to one male, or actually of 310 females and 161 males. This ratio is very difficult to interpret and particularly in regard to etiology. Probably one-third to one-half of the very sick people in this country do not have the interpretative benefit of a blood count and further studies may change this ratio. Of our 12 cases, eight were women and four, strong men.

A case in point was that of a school teacher that one of us (S. R. R.) was called in to see in 1927. She had already previously been seen by two physicians, but although the patient was very ill and had become unconscious, no blood examination had been made. Had she been a nurse, she would doubtless have been taken to the hospital at the beginning of her illness and the diagnosis been made promptly. As it was, the disease was overlooked, and the diagnosis made of streptococcic throat was in error. A majority of people who die in the world never have had the benefit of a blood examination. We do not know how many people have complete granulopenia and must resist the temptation to leap to a speedy conclusion from a very limited experience over a very short period of time.

Social Incidence

It is apparent thus far that a majority of cases reported appear among those in the middle and upper classes, in the higher economic and cultural levels. On the other hand, the great majority of people on the lower economic levels postpone treatment, or may not see a physician until necrosis of the throat is so far advanced as to permit a glib diagnosis of malignant sore throat, or have no hospital facilities and no opportunity to receive a correct diagnosis. More facts are necessary for a conclusion involving social incidence. In American medicine one does well to remember that there are 125 million people in the United States and that many millions of them do not have the benefit of any modern medical facilities, much less adequate medical care.

Occupation

The following table shows the occupation of 250 of the 473 cases in the United States. In 223 cases data as to occupation are not furnished. Conclusions, or even intimations, from such a table are scarcely warranted. However, it is apparent that to date the disease has appeared most frequently in housewives and in persons falling into the medical group.

Table II

Housewives	102
Physicians	22
Nurses	17
Hospital employees	4
Medical students	3
Laboratory technicians	1
Relatives of physicians	11
School teachers	2
Farmers	5
Business men—all types	10
Sixty other occupations (each)	1 or 2

Many have noted this predilection of the disease for physicians and their families, nurses, medical students, technicians and others of the medical group. It has been commented upon in the papers of Kracke [17, 21] and by Stellhorn and Amolsch.[7] Among Harkins' [5] eight cases there were a doctor, a medical student and a nurse. In Madison and Squier's [6] series of 14 cases there were five in the medical group counting the wives of two physicians; and the authors write, "In this group (of cases) as in the disease at large, there seems to be a remarkable relation to the medical and allied professions." This statement undoubtedly applies to the group of cases they reported but probably does not apply, in the same proportion, to "the disease at large." In our group of 12 cases, for example, there were only two, a physician and a nurse, from the medical group. It is true that of the males reported 13.6 per cent are physicians and of the females 5.4 per cent are nurses. A factor of some importance in determining this rather large percentage of the medical group is that sick doctors and nurses go more quickly to hospital in our experience than do others and more quickly receive the benefit of repeated laboratory examinations and consultations. In the medical group so rare a disease or so baffling a case would probably receive the most thorough study and the quickest diagnosis.

Comment is certainly justified upon the fact that the disease has occurred most frequently in women and especially among those classified as housewives; of the eight women in our series seven were in this occupation, if it may be so called. To date the data from reported cases allow of no difference of opinion on these points.

Present Ideas of Etiology

The cause of the disease is unknown. From the present evidence, there seems to be no single etiological factor that fits every case, nor has it been proved that any of the possible causes that have been suggested are responsible for the disease. With a new disease one fishes quickly in the pond of cause and effect in the hope that the prize fish of etiology may soon swallow bait, hook and sinker. All these excursions ultimately will result in the discovery and proof of the etiology. One steps very carefully here. Coincidence does not necessarily mean proof. Different points of view, clinical observations and experiments with animals all produce positive or negative evidence, and all are valuable. The various suggestions as to etiology offered by students of the disease are summarized in the following table:

Table III

1. Specific bacterial etiology: nothing conclusive discovered.
2. Abnormal menstrual states.
3. Certain anemias, aplastic, pernicious and secondary.
4. After leukopenic diseases, as influenza.
5. Certain drugs, as arsphenamine, amidopyrine and benzene ring compounds.
6. Exhaustive states, induced by toil, worry, and mental effort.
7. Certain senile states in asthenic women.

1. Bacteria. Since Lovett [8] reported the first case of this disease in the United States many studies have been made in an effort to incriminate a specific bacterium. She attempted to show that the *Bacillus pyocyaneous,* which she found in the oral ulcers of her patient, was responsible, but without success. Since that time much experimental work has been done with bacteria in an effort to reproduce the disease in laboratory animals but it has been uniformly unsuccessful. Many of the bacteria involved have been the various streptococci, the *Bacillus pyocyaneous,* bacillus of hog cholera, dead and living typhoid bacilli, Vincent's organisms, etc. Many writers have stated that various degrees of granulopenia have been produced in laboratory animals with these organisms but apparently they did not take into account the fact that transient and temporarily severe leukopenic states can be produced with nearly any and all bacteria, dead or living. A significant contribution is that of Dennis,[9] who was able to produce a prolonged granulopenia by the introduction of *Streptococcus viridans* in parchment capsules into the peritoneal cavity of rabbits. One of us (R. R. K.) has repeated, in so far as possible, this work and is unable to confirm the results of Dennis.

There seems no evidence that there is a specific bacterial etiology. Positive blood cultures were obtained in about 20 per cent of the total number of cases; they were positive in 70 per cent of the cases on whom cultures were taken. The streptococci were by far the most frequent invaders. There were 74 positive cultures and 395 cases in which cultures were either negative, or not stated as taken. The data in table 4 illustrate this point in detail.

There is no more reason to suspect a bacterium to be the cause of this disease than to suspect a specific bacterium to be the cause of aplastic anemia. On the other hand, as we [1] have shown in our first paper, the blood stream infection is probably secondary to the leukopenic state. One must keep the horse of acute granulopenia with the loss of immunity to bacterial invasion ahead of the cart of the secondary bacterial invasion. This explains why so many different bacteria are recovered in blood cultures. This explains why the usual surgical treatment of the secondary infection and necrosis is so unavailing. This explains in terms of treatment why this secondary infection, particularly with pus producing bacteria, is the chief therapeutic hope of the patient, because it is nature's method of quickly arousing a leukocytosis.

2. Hubble [10] suggests that glandular dysfunction may play a rôle in producing the disease and suggests that bone marrow depression may be caused by a pituitary basophilic insufficiency or granulopenia by cortical adrenal dysfunction. Corey and Britton [11] observed an agranulopenic syndrome in adrenalectomized cats and Thompson [12] believes that the disorder may be associated in some way with the glandular changes of menstruation. Thompson's studies are worthy of serious consideration. Our case 8 was afflicted with menorrhagia as well as great toil and worry. The temptation may be to dismiss these suggestions as too speculative.

TABLE IV

Blood Stream Infection in Granulopenia

Organism	Number of Cases
Streptococcus hemolyticus	8
Streptococcus viridans	15
Streptococcus (type undetermined)	9
Staphylococcus albus	3
Staphylococcus aureus	4
Bacillus Friedlander	4
Pneumococcus, type 2	3
Pneumococcus, type 3	1
Pneumococcus, type 4	2
Pneumococcus, type undetermined	2
Diplococcus (undetermined)	4
Bacillus pyocyaneous	3
Bacillus paratyphosus B	1
Bacillus coli	3
Bacillus proteus	1
Streptothrix	3
Streptococcus with other bacteria	9
Fusiform bacillus (Gram negative)	1
Estivo-autumnal parasite	1
Various cocci	3
Staphylococcus (undetermined)	1
Diphtheria bacillus	1
Vincent's organisms	1
Typhoid bacillus	1
Bacillus (undetermined)	1
Total number of positive cultures	74
Negative, or not stated	395

3. The possible relation to certain blood diseases is discussed under the heading of " Relation to Other Diseases." Suffice it to say here that other anemias may depress the myelocytic function of the marrow with a resulting granulopenia. Such a granulopenia may thus invite bacterial invasion and hasten death. We have seen this in a case of acute lymphatic leukemia. It is common in aplastic anemia to see a granulopenia.

4. Cases 2, 5 and 7 of our series followed influenza in an influenza epidemic. We have before pointed out the great weakness and prostration in the acute infections characterized by granulopenia.

5. There has been much recent discussion following the suggestion that arsphenamine, amidopyrine and benzene ring compounds may cause the disease. Much of the discussion about the relative frequency of the disease in the medical group of occupations, i.e., doctors, nurses, technicians, etc., finds its point here. The granulopenic state following arsphenamine administration in certain cases has long been recognized. The frequency of granulopenia in those treated with gold salts for tuberculosis has been observed by several French writers.[13, 14, 15] The possible rôle of certain coal tar drugs in the production of the disease has been stressed by Kracke.[16, 17] Madison and Squier [6] have presented evidence that all of their cases were given drugs of this class preceding the clinical onset. Chief among these drugs under suspicion at this time is amidopyrine alone or in combination

with a barbiturate. On the other hand, Thompson [18] states that he has carefully investigated the histories of his 46 cases of granulopenia and that there is no evidence to incriminate either amidopyrine or the barbiturates. Circumstantial evidence continues to accumulate that amidopyrine in certain cases has power to depress the myelocytic function of the bone marrow.[23] This is certainly not true, however, of all persons to whom amidopyrine is administered. These differences in myelocytic response to amidopyrine intimate therefore that the myelocytic function of the bone marrow varies in the degree of its sensitivity. Pepper [19] refers to the allergic predisposition of individuals who have granulopenia. We have not confirmed his suggestion in our series. Perhaps one who has granulopenia may have a weakened or inferior marrow which may be hypersensitive to allergic influences, but this would be very difficult of proof.

Exhaustive States

It is curious that cases 1, 2, 3, 4, 6, and 10 of our 12 cases, and another case reserved for a later report, and not included in this series, were lean, pale, asthenic women of little reserve. Each of them lived on a lower level of strength and activity than normal and one could well call them frail, exhausted women. Their families spoke of them as "lacking strength, complaining of weakness and unable to stand much strain." Most of them were of middle age or older and physically below par with a hemoglobin ranging from 60 to 70 before granulopenia developed. One can only speculate here that the bone marrow, viewed as an organ, may become selectively exhausted or disturbed to such a degree that normal function is impossible. There is selective failure of the myelocytic function of the bone marrow. We have seen erythrocytic failure repeatedly in senile hypochromic anemia. Cases 8 and 11 of our series had their attacks after prolonged toil, loss of sleep and great worry and each of them had been warned long before the attack that she could not continue to work so hard. Women of a certain asthenic type and women of great toil form a suggestive group.

The Hemorrhagic Trend in Complete Granulopenia

In the reports of the postmortem examinations one finds recurring references to hemorrhages both dermal and visceral. A study of this hemorrhagic tendency affords material for a good paper. We have seen during the course of the disease petechiae on the conjunctiva, the oral and rectal mucosa, the skin, then larger purpuric areas even to a massive purpuric area involving one-third the trunk. Bleeding may occur from the nose, throat, alimentary tract, urinary tract, uterus and vagina. Such bleeding is as a rule small in amount. We have seen at postmortem examination petechial and larger hemorrhages in the lungs, subpleural hemorrhages, and petechiae in the epicardium, endocardium, stomach and intestines.[22] In one case

there was an acute hemorrhagic splenitis. Sepsis may be an important factor in the production of these hemorrhages. The platelets may show a marked decrease. No hemorrhages may be seen during life and yet necropsy may reveal many. It is rare to see a case in which there is not some manifestation of this hemorrhagic trend. With large purpuric areas the superficial likeness to purpura may confuse the diagnosis and we have seen this mistake made once. This tendency to hemorrhage probably arises from a bone marrow dysfunction involving the megakaryocytes and a decrease in platelet formation. Complete granulopenia may masquerade with a purpuric front. Careful blood studies tell the story. Purpura hemorrhagica may be cured with transfusion or splenectomy, but not a complete granulopenia.

Report of Twelve Cases

The following 12 cases, only one of which has been previously reported, illustrate definite points in the disease. We have another case for a future report because there have been two attacks and we have followed the blood carefully over a period of two years.

The more one studies these cases and the hemograms, the more the evidence points to the reappearance of granulocytes in the blood stream as the one chief purpose of treatment and the one hope of recovery. Table 5 gives a condensed summary of these 12 cases, and the history of each case more in detail follows:

Case Reports

Case 1. Mrs. W. W. F., aged 46, a patient of Dr. W. F. Shallenberger, had five cystoscopic examinations during 1928. Otherwise she appeared well. Four days after the last examination on November 16, 1928, she became extremely weak, an unexplained fever developed and she died on the third day with a leukocyte count of 400 cells.

Case 2. Mrs. L. Z. R., aged 72, an asthenic woman with a chronic secondary anemia, developed on March 12, 1929 fever, prostration, a red, edematous and quickly necrotic throat, and a white cell count of 2,000 with no granulocytes. She was unconscious and delirious, with a profuse diarrhea. Concurrent with the development of embolic abscesses in the skin and deep abscesses in the muscle of the calf, she showed a widespread infection with the *Streptococcus hemolyticus* in the blood stream, skin and muscle abscesses. Despite the previous absence of granulocytes for days, myelocytes and juvenile forms began to appear in the blood stream after the abscesses developed, and in eight days she had a leukocyte count of 41,000 with 84 per cent granulocytes. She had been convalescent for 65 days and appeared to be in better health than formerly, when the white cell count quickly dropped to 400 with complete absence of granulocytes and she died on the fourth day of the second attack.

This case has previously been reported in detail, and affords proof that the bone marrow in severe acute complete granulopenia may not be irreparably damaged, but with time and stimulation of myelocytic activity may still be capable of normal function. We believe that the stimulation in this

TABLE V

Case	Sex	Race	Age	Occupation	W.B.C.	R.B.C.	Platelets	Hemorrhage	Bone Marrow Regeneration*	Terminal Infection	Result
1	F.	W.	46	H. W.	400			None	Died 1st attack	None	Died
2**	F.	W.	72	Ret. H. W.	400	3,500,000	Normal	None	Yes	Strep. hemo.	Died 2nd attack
3	F.	W.	34	H. W.	450	4,000,000	Normal	None	No	No	Died
4**	F.	W.	44	H. W.	470	5,200,000	Normal	None	Yes	No	Died 3rd attack
5	M.	W.	50	Physician	400	3,160,000	Normal	None	No	Broncho-pneumonia	Died
6	F.	W.	35	H. W.	400	2,800,000	Decreased	Yes	No	No	Died
7	M.	W.	64	Police chief	950	3,700,000	Normal	No	No	No	Died
8	F.	W.	48	Librarian	450	4,300,000	Normal	No	No	Strep. hemo.	Died
9	M.	W.	50	Mill-worker	450	5,600,000	Normal	No	Yes	No	Died 2nd attack
10	F.	W.	38	H. W.	450	4,800,000	Normal	No	Yes	No	Recovered
11	F.	W.	26	Nurse	300	4,900,000	Normal	No	No	Yes	Died
12	M.	W.	42	Business man	200	4,300,000	Normal	No	No	No	Died

* Bone marrow regeneration refers to development of leukocytosis after granulopenic attack.
** Case previously reported in detail.

case was due to the infection with *Streptococcus hemolyticus*. This case also proves that the fall and absence of the granulocytes precedes by one or more days the clinical onset of the disease.

Case 3. Mrs. R. G., aged 34, had influenza in early March of 1931. She had been weak and unable to resume her usual activity. She had run a slight post-influenzal temperature and on April 7 was confined to her bed on account of weakness and fever. The leukocyte count was only 2,000 and granulocytes were absent. The course of the disease was septic and stormy and death occurred on the seventh day with a total white count of 450, all lymphocytes. Postmortem examination showed a hypoplastic bone marrow, patched yellow and red, with numerous subpleural and subperitoneal petechial hemorrhages.

This case illustrates severe acute complete granulopenia, a normal platelet count, no clinical evidence of hemorrhage and yet multiple small hemorrhages at necropsy.

Case 4. Mrs. F. P. S. was an asthenic woman who had long suffered with methemoglobinemia and its characteristic slate blue color. For some weeks she had complained of weakness and fever and had presented evidence of mild sepsis. Her leukocyte count was 900 with no granulocytes. The count gradually fell to 470 and rose during the next 25 days to 5100 leukocytes with 80 per cent granulocytes. This attack began on May 13, 1930. On June 30, 1930, 48 days later, she developed a pleurisy with effusion, with a leukocyte count of only 2500. On July 16 her leukocyte count had risen to 4000. A third attack of granulopenia occurred on November 22, 1930 with a total leukocyte count of only 200, entire absence of granulocytes, and death the next day, November 23, 1930.

This case illustrates again that the bone marrow is capable of regeneration within limits. The woman recovered from two attacks only to die in the third. It also shows the association of methemoglobinemia with complete granulopenia. She gave a history of having taken phenacetin for the three previous years and this was probably the cause of the methemoglobinemia.

Case 5. Dr. C. E. S., physician, 50 years of age, was taken acutely ill on April 9, 1931, with a leukocyte count of 1450, and no granulocytes. He had done a heavy practice for the preceding six months by day and night and in the middle of March had suffered a rather severe attack of influenza. He ran a stormy septic course in his final illness with a gradual fall in the granulocytes and died on the fifth day of a terminal bronchopneumonia with a total white count of only 400. There was necrosis and edema of the throat. Purpuric areas developed over the elbows. During a transfusion, blood was seen to pass outward through the wall of the median basilic vein and infiltrate the surrounding tissues. Purpuric areas appeared at once on the adjacent skin. The blood pressure was 125 systolic and 100 diastolic. His liver and spleen both were palpable. Hiccoughs were frequent. Profuse diarrhea and emesis occurred; and moderate delirium alternating with periods of orientation were noted. Necropsy was refused.

This case illustrates the damage done to at least one vein. He probably had many hemorrhages throughout the body. It is noteworthy that the case followed influenza, and the influenza followed a period of great exhaustion.

Case 6. Mrs. M. N., aged 35, fell ill on April 18, 1931 with a necrosis of the throat following acute follicular tonsillitis which had lasted for 18 days. For the 10 days previous to April 18 and the onset of the necrosis, her temperature had averaged 103°. She was prostrated with weakness. Her leukocyte count was 2100 with 2 per cent granulocytes. There was a stormy course with sepsis and hemorrhages and she died on the eighth day with a total white count of 400 and no granulocytes. The necropsy showed many hemorrhages in the skin, subcutaneous tissues and viscera.

This case illustrates the hemorrhagic trend associated with complete granulopenia and its secondary sepsis. The platelets were only slightly decreased. Sepsis followed the granulopenia. The bone marrow did not respond to the stimulation of the sepsis.

Case 7. Mr. M. D. G., aged 64, chief of police, had been in excellent health for the past year. One week before his acute attack of granulopenia he had influenza. On March 7, 1930 he had fever and was weak and felt badly. On March 8, he had a chill and his throat was red. On March 9, he had a total leukocyte count of 2260 with no granulocytes. He died 48 hours later with a count of 950. There was no evidence of necrosis.

This case illustrates that an acute complete granulopenia may come like a storm, run a rapid course and cause death in four days with no evidence of necrosis. He had no visible evidence of infection at any time save the redness of the throat. There was hardly time for sepsis to develop. The cause of death was evidently the mere absence of the granulocytes.

Case 8. Miss M. L., librarian, 48 years of age. For the past three months she had nursed both of her aged parents, done all the house work including the cooking and washing, worried much, was in the menopause and had suffered two moderate uterine hemorrhages. On August 12, 1934, she began to feel ill and noticed that her throat was red and slightly sore. She became weaker, with increasing redness of the throat and more and more prostration, and on August 15, 1932, a hemogram showed a total leukocyte count of only 950, with no granulocytes. She showed the characteristic physical prostration, and mental dullness varying from delirium to coma. She died on August 20 with a leukocyte count of 450; not a granulocyte was seen during the entire course of her illness. A *Streptococcus hemolyticus* was isolated from the blood stream. Necrosis and edema of the throat were extreme. Necropsy results were unimportant except that a gas bacillus was cultured from the necropsy blood.

This case illustrates acute complete granulopenia following a long period of exhaustion, and associated with two previous moderate uterine hemorrhages.

Case 9. Mr. F. S., mill worker, 50 years of age, was admitted to the hospital on February 23, 1931, complaining of pain in the lower left quadrant of the abdomen of two months' duration. His blood count showed 8500 leukocytes with 60 per cent granulocytes. A diarrhea was present, and examination revealed multiple superficial ulcers in the sigmoid and rectum. His liver and spleen were palpable. On April 2 his leukocyte count had fallen to 1500 with only 2 per cent granulocytes. Sepsis developed with necrosis in the mouth and throat. A sternal puncture was done and the examination of the bone marrow revealed marked hyperplasia and not aplasia. Four days later the total leukocyte count had quickly risen to 22,000 with 70 per cent

granulocytes. The patient was, of course, much improved. The leukocyte count continued normal or above until May 29, when it quickly fell to 600 leukocytes with no granulocytes and the patient died the next day. During the first attack there was also necrosis at the anal margin.

This case illustrates two attacks of granulopenia. The patient recovered from the first attack because the myelocytic function of the bone marrow was resumed. His sternal puncture and bone marrow study were made during the first attack, but at a time when the marrow had resumed its activity and become hyperplastic. This is proved by the fact that myeloblasts, premyelocytes and myelocytes were found in the bone marrow smear at a time when the peripheral cell count was only 450 with no granulocytes. The condition of the bone marrow resulted four days later in a total leukocyte count of 22,000. At necropsy following death in the second attack, the bone marrow was markedly aplastic. The patient had died because the bone marrow in the second attack did not resume its myelocytic function, and granulocytes did not appear in the blood stream.

Case 10. Mrs. A. L. K., aged 38, a patient of Dr. Trimble Johnson, whom we saw in consultation, entered the Emory University Hospital on March 30, 1933, complaining of fatigue and sore throat of several years' duration. She was an asthenic woman with a reddened throat and small pharyngeal ulcers. The total leukocyte count was 950, and no granulocytes were seen. The leukocyte count remained at this level for three days, during which she ran a septic temperature and quickly developed a deep necrosis of the left foot and the lower one-third of the leg. In five days the leukocyte count had risen to 30,250 with a predominance of granulocytes and myelocytes. During the next 30 days the leukocyte count gradually fell to normal and the foot and leg gradually healed. There was much sloughing of the necrotic area. She is still well, one year after recovery from the first attack.

It seems to us that the chief factor in her treatment was the development of the extensive necrosis and gangrene of the left foot with its coincident stimulation of the bone marrow. The organisms isolated from the necrotic area were all pyogenic in type. This necrosis and these pyogenic bacteria confirm our conception that infection is secondary to the granulopenia and that the patient's chief chance of recovery is afforded through the secondary infection itself.

Case 11. Miss S. K., white female, aged 26, a nurse, patient of Dr. C. W. Strickler and Dr. Lon W. Grove, whom we saw in consultation, had been working very hard for the past several months. She was admitted to the Emory University Hospital September 9, 1933, complaining of weakness, general aching, fever and chill occurring the previous day. Physical examination was negative except that she had had a superficial skin eruption of the fingers of the right hand. The total leukocyte count was 2,000 with 4 per cent granulocytes. She grew rapidly worse, sepsis developing with high fever, and necrosis and edema of the right hand. Death occurred on the seventh day with a total leukocyte count of 300, with no granulocytes. The blood cultures were negative.

This is the second case we have seen which had a chill. There had been a mild vesicular eruption of the right hand with superficial ulceration; the

necrosis took hold here rapidly and deeply, and the edema extended quickly as high as the right axilla. Even with such inflammation and necrosis the bone marrow did not respond to its stimulation.

Case 12. Mr. J. P. M., aged 42, executive, patient of Dr. J. P. Tye of Albany, Ga., entered the hospital on January 16, 1934 with marked weakness, physical prostration and a red and edematous throat. One year previously his physician had told him that he had a low white cell count. During the past year he had suffered with multiple arthritis. For eight days he ran a stormy septic course, with increasing fever and progressive weakness. The total leukocyte count dropped to 400 with no granulocytes. Death occurred on the eighth day.

Here was an instance of the disease attacking a strong, though slightly obese, individual, a man of great muscular development, a former football star, who had lived a vigorous outdoor life up to his last illness, with the exception of the limitations imposed by the moderate multiple arthritis. Two of our cases were of this type and both died. Here was acute complete granulopenia that ran a stormy course with complete myelocytic failure.

The Cause of Death

Nature has certain requirements for the existence of the individual. Oxygen, for example, is necessary for life. There is so little reserve of oxygen in the tissues and the need for it is so urgent and imperative, that one can hold one's breath only for about a minute or less. Similarly, the granulocytes seem necessary for the existence of the individual. Complete granulopenia seems to be the first disease that has almost dramatically forced this fact to our attention. One may live with 2,000 or 200,000 granulocytes but without them there can be no life. As a rule, in proportion as the granulocytes fall below the normal level, so does robust living lessen. Nature appears to have given the granulocytes a wider amplitude of daily variation than any other cell of the blood. The count may dip and rise under many influences. Normally they vary with the daily ebb and flow, but in time of need they rise with exercise, inflammation, excitement and even food. The granulocyte may be regarded as a highly specialized cell with multiple functions. These cells and these functions are necessary for life.

1. One function seems to be to confer upon the tissues of the normal individual an ever present daily immunity to bacterial invasion. In complete granulopenia this immunity is lost, and one to four days after the granulocytes disappear from the blood stream, bacterial invasion usually proceeds rapidly. This invasion is stopped and the living bacteria in the blood stream and tissues cease their activity and die, or are eliminated, only by the reappearance of granulocytes in the blood stream. Without granulocytes there is sepsis, and with sepsis there is death unless the granulocytes reappear.

2. It seems that the presence of the granulocytes is necessary to the individual for the maintenance of his daily normal strength. In complete

granulopenia, even before bacterial invasion has taken place, we have repeatedly seen the quick phases of fatigue, exhaustion, prostration and even collapse. We have seen this progressive loss of strength in our first case and consistently in all the subsequent cases. It is bedside observation with proof. The longer the granulocytes are absent, the greater the prostration. This prostration may be contrasted with the maniacal struggles of the patient with meningitis and with leukocytosis, or the thyroid-like activity of the patient with subacute bacterial endocarditis.

3. Concurrent with this loss of strength, perhaps as a part of the same process, and likewise before bacterial invasion, there is a dulling of the mental functions, a falling away of the normal vividness and awareness of the immediate surroundings, a loss of memory, a sleepy silence, then a muttering delirium or a deep unconsciousness. Memory is gone days before death comes.

4. No one has yet accounted for the rising fever of complete granulopenia that comes before sepsis. It is very difficult to state when sepsis begins and one can note its beginning with only relative accuracy. With immunity gone, one does not know how quickly bacteria invade the intestinal wall and pass to the adjacent tissues. The appearance of multiple ulcers in the intestinal mucosa is probably synchronous with the necrosis of the mouth, throat and rectum. Nevertheless, this curious fever precedes the evidence of sepsis. This fact seems to intimate that one of the functions of the granulocytes may be to aid in heat control.

With the loss of immunity to bacteria, the loss of strength, the prostration of the mental functions, the rising fever, and then a quick sepsis, death is inevitable unless a new crop of granulocytes quickly comes back into the blood stream. If in this time of sepsis, the bone marrow reassumes its myelocytic activity, the first evidence in the blood stream is the finding of juveniles and band forms of the granulocytes, myelocytes and in one case myeloblasts. In case 10 myelocytes appeared in the blood two days before any juvenile granulocytes were seen. On the third day of regeneration there were 1350 leukocytes, of which 64 per cent were myelocytes, 8 per cent each of juvenile and band forms, and 20 per cent lymphocytes. Such a preponderance of myelocytes intimates nature's hurry to cure by the only known method—new granulocytes. Without them, sepsis does its perfect work through a blood stream infection, necrosis and gangrene, perhaps hemorrhage, intestinal ulceration, with or without a diarrhea, furunculosis, visceral abscesses, circulatory failure and a terminal bronchopneumonia. Here bronchopneumonia may better be regarded as a combination of localized pulmonary sepsis and circulatory failure.

Treatment

Acute incomplete granulopenia is as a rule a far milder condition than the usual fatal acute complete granulopenia. Some authors have not dis-

tinguished between the danger of the two conditions. All 12 of the cases reported in this paper showed an entire absence of granulocytes and were therefore acute complete granulopenias. Ten of the 12 are dead. Only two are living, both women, and one has had two attacks. As long as granulocytes remain in the blood stream, there is probably some myelocytic activity. The resumption of normal activity is a matter of degree of function and the prognosis is more favorable. Good nursing, food, water, fresh air and a watchful, expectant attitude may be all that is wise. The tendency is to do too much and to continue to do too much. Wise clinical judgment at the bedside is better than much long distance telephoning to distant authorities who boost a new and single specific remedy.

It is quite different with a complete granulopenia that comes with the sweep of a clinical storm. The mechanism and series of events in this degree of granulopenia are of ill import for recovery. Complete granulopenia is usually a fatal disease during the first or a later attack. We have not seen either of our two recovered cases return to normal, robust health. An absence of granulocytes in the blood stream means that the bone marrow has ceased its myelocytic activity and that collapse, fever, loss of immunity to bacteria and sepsis are at hand. One is called to treat far more than the apparently simple condition of absent granulocytes. Those who advocate and use specific remedies would do well to realize the enormous power they are claiming for the remedy. What is needed here is judgment of the therapeutic proof by the standards of scientific accuracy.

There are three chief objectives of scientific treatment:

1. The maintenance of the life and strength of the patient; much can be done with good nursing, food, air, water and care of the skin, throat, and control of fever.

2. The stimulation of the bone marrow to such a degree that it may resume its myeloblastic activity with the production of myelocytes and granulocytes. So far as we know, granulocytes do not function until they slip into the blood stream. There is apparently no known drug or specific remedy that can thus sufficiently stimulate the bone marrow.

3. The invitation to an early sepsis as nature's most universally used method to stimulate the myeloblastic activity of the marrow. It is the quickest way known to produce a leukocytosis. Nature uses it with telling effect in nearly all the purulent infections with pyogenic bacteria. The leukocytosis of appendicitis is an example. It is a myeloblastic stimulation that the surgeon calls a leukocytosis. There is no better way to provide it than the way nature provides it. We take the position that even complete granulopenia does not necessarily irreparably damage the marrow to the extent of destroying this important function. The function is in abeyance. After necrosis and sepsis we have seen the granulocytes rise in four days from none to 40,000. In another case with necrosis of the foot, in four days the granulocytes rose to 25,000.

With absent granulocytes and increasing sepsis, it is merely a question whether the patient can survive long enough for the granulocytes to reappear. Sepsis and necrosis are the great hopes of every patient with complete granulopenia. The patient may die from sepsis with maturation proceeding at full tilt in the marrow, but before the granulocytes reach the blood stream. It is well to avoid surgical treatment of the necrotic areas. Such treatment is of no avail until the granulocytes appear in the blood stream, and their reappearance will usually cure the patient and also the sepsis and necrosis.

With no evidence of sepsis and necrosis, one would not do far wrong to inject living staphylococci in the skin, or give 5 to 10 minim doses of turpentine intramuscularly. Kracke has shown that turpentine in this way causes necrosis of muscle tissue and a leukocytosis in the rabbit. One of us (S. R. R.) used this method in one of our surviving cases apparently with a happy effect.

We have used radiation, transfusion, liver extract, pentose nucleotide and foreign protein to no avail. We have seen no result and only disappointment from their use. We have had no experience with adenin sulphate. We see no reason why it should be of aid.

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DRUG IDIOSYNCRASY, WITH SPECIAL REFERENCE TO AMIDOPYRINE, AS A CAUSE OF AGRANULOCYTIC ANGINA *

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THE designation, agranulocytic angina, although etymologically incorrect and scientifically inept, has become firmly entrenched—despite other preferable designations such as "pernicious leukopenia" or "primary granulocytopenia." It is here employed, in the now generally accepted sense, as designating the syndrome of Schultz. This disorder was at first viewed as a peculiar reaction to some unknown infection, analogous to the previously recognized leukopenia sometimes encountered in overwhelming sepsis. Soon, however, it became clear that the heterogeneous microorganismal invasion, seen in the majority of cases of agranulocytic angina, is merely a secondary or terminal event and is preceded by profound neutropenia. This led to the current view of agranulocytic angina as a clinicopathologic entity of undetermined etiology belonging to the group of "blood system diseases"—to be distinguished from, although often simulated by, other types of neutropenia.

The possibility of an allergic mechanism in the etiology of agranulocytic angina has been emphasized in clinical teaching by O. H. P. Pepper since 1928 (after observing several patients afflicted with this disease whose histories indicated clear-cut allergic backgrounds). His first recorded statement of this hypothesis was made April 16, 1930, before the College of Physicians of Philadelphia [1] and was presented in greater detail in a Black Memorial Lecture [2] at Pasadena in January 1931. In a review of 18 cases of agranulocytic angina published in April 1933 Fitz-Hugh and Comroe [3] stated that "additional treatment in all cases included oropharyngeal care, avoidance of drugs that might reasonably produce anaphylactoid reaction (Dr. Pepper's suggestion), the use of orange juice, vitavose, calcium gluconate, and cod-liver oil." Following the publication of this article with its specific reference to the possibility of "anaphylactoid" drug dangers, there appeared, quite independently, the epoch-making contribution of Madison and Squier [4] presenting very strong evidence tending to incriminate amidopyrine medication with resulting allergic or anaphylactoid reaction as a most important cause of agranulocytic angina. Similar reports, altogether constituting a grave indictment of amidopyrine with or without barbiturates, have since rapidly accumulated.[5, 6, 7, 8, 9, 10]

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The recent comprehensive review by Kracke and Parker [9] of the hypotheses, experimental data, and clinical and laboratory findings relating to etiology makes unnecessary any general recapitulation. Since 1930 Kracke has maintained that drugs containing the benzene ring may be responsible for the disease and especially those belonging to the "benzamine group": amidopyrine, phenacetin, acetanilid, arsphenamine, neoarsphenamine. He has viewed this mechanism as a direct toxic action of some one or more of the oxidation products of benzene (hydroquinone, catechol, orthoquinone and paraquinone) on the bone marrow. His present position, however, includes the hypothesis of a "previously weakened, damaged, or idiosyncratic bone marrow" to account for the obvious facts that only a very few of the many individuals exposed to these substances actually develop the disease, and only an occasional experimental animal exhibits granulocytopenia out of a large group of animals given these drugs or their oxidation products.

In spite of the fact that our clinical staff has been for the past six years aware of the possibility of drug idiosyncrasy in agranulocytic angina and has frequently forbidden this or that drug in any given case where there seemed to be a suggestion in the patient's history of such drug's unfavorable or unusual action (including "allonal" in one early case!), we nevertheless failed completely to recognize the apparently important rôle of amidopyrine until the findings of Madison and Squier came to our attention a few months prior to publication of their paper. The purpose of the present report is to summarize the evidence accumulated in a review of our cases from the standpoint of drug idiosyncrasy, with especial reference to amidopyrine, as a possible cause of agranulocytic angina.

The following statistics and observations are based on a study of 26 cases of agranulocytic angina of which 18 have been previously reported.[3] These data were obtained by study of recent patients, by review of hospital and office records, by personal conferences with surviving patients, and by correspondence with patients, relatives, and referring physicians.

The sequence of amidopyrine medication followed by hematologic proof of the diagnosis of agranulocytic angina is present in 14 cases (54 per cent). This same sequence is probably present but unproved in another five cases (19 per cent) and entirely unproved (but not impossible) in another six cases (23 per cent). The sequence is disproved in one case only.

In addition to the 14 proved instances of amidopyrine medication prior to hematologic verification of the disease (seven of whom continued the drug) there are three instances of amidopyrine medication instituted during the course of the disease. Thus 17 patients (65 per cent) are known to have ingested amidopyrine just prior to and/or during the course of the hematologically manifest stage of the disease. Of these 17 patients 13 are dead of the disease (77 per cent mortality) and four are living and well. Of the 13 fatal cases 10 continued and three discontinued ingestion of amidopyrine immediately after the establishment of the diagnosis. Of the

four surviving patients in this group three discontinued at once the ingestion of amidopyrine on establishment of the diagnosis and one discontinued it soon thereafter.

Of the five cases listed as "probable but unproved" in relation to prior amidopyrine medication four are dead and three of these received amidopyrine during the course of the disease. Of the six "unproved" cases five died (all "acute cases") without receiving any amidopyrine after hematologic verification of the disease, although the possibility of prior amidopyrine medication can neither be affirmed nor denied with absolute certainty.

The one patient in this series in whom amidopyrine medication can be absolutely excluded from all consideration will be discussed in some detail below. The total mortality figures to date are: 19 dead (73 per cent); one of unknown status; and six living (three weeks' "cure," six months' "cure," eight months' "cure," three years' "cure," five years' "cure," and one relapsing case at present in good condition).

The preparations containing amidopyrine ingested by these patients are: amidopyrine in capsule with other ingredients as prescribed by attending physicians; "pyramidon"; "allonal"; "peralga"; "amytal compound"; and "midol tablets." * In no instance has the dosage of the drug been in excess of the average therapeutic limit. The largest quantity known to have been taken by any one of these patients was 25 grains daily of amidopyrine for seven days immediately prior to hospitalization, when the diagnosis was established. Two patients had used "allonal" and "pyramidon" at irregular intervals and in ordinary therapeutic quantity for several years before the fatal agranulocytic episode which seemed to follow just one more "ordinary dose." One patient had taken a few "midol tablets" for a few days each month for about six months prior to the proved onset of the disease. Another had taken only two "allonal" tablets and four "pyramidon" tablets during the period of 48 hours between a tooth extraction and the proved hematologic onset of agranulocytosis. Another, because of "acute tonsillitis," took a capsule containing two grains of amidopyrine every four hours for three days at the end of which period agranulocytosis was discovered. Our most recent case is that of a pupil-nurse who had taken one to two tablets of pyramidon once a month for about five years for relief of headaches. She had taken none, however, for at least a month until 5–29–34 when she took two tablets and repeated this dose (10 grains) on 5–30–34. Profound neutropenia was discovered on this date. A week later, after hematologic and clinical recovery, this patient was given

* A partial list, alphabetically arranged, of proprietary and patented medicaments in which available evidence indicates an amidopyrine content includes: "Allonal," "Alphebin," "Amarbital," "Amido-Neonal," "Amidophen," "Amifeine," "Am-Phen-Al," "Ampydin," "Amytal Compound," "Baramid," "Barbromide" (Columbus), "Benzedo Compound," "Cibalgine," "Cincopyrine," "Compral," "Dysco," "Gynalgos," "Hexin," "Ipral-amidopyrine," "Kalms," "Lumordrin," "Midol," "Mylin," "Neonal Compound," "Neurodyne," "Optalidon," "Peralga," "Phenamidal," "Pyramidon," "Pyraminal," "Sal-Ethyl Carbonate Compound."

one five-grain tablet of amidopyrine with an ensuing loss of more than one-third of her circulating neutrophiles in three hours, followed by prompt recovery.

It is obvious that if amidopyrine-idiosyncrasy is a cause of agranulocytic angina we shall have to revise some of our concepts of the disease. In the first place the earliest symptoms of ill health, instead of being true "onset symptoms" of the disease itself in many instances must be viewed as purely accidental disorders which occasion the use of amidopyrine (or other drug) medication. This conclusion is predicated on the fact that several patients had taken no medicine of any kind for many months prior to the onset of distress symptoms which then, and then only, were met with drug (amidopyrine) administration and which seemed to merge promptly and imperceptibly into the ensuing picture of hematologically established agranulocytic angina. Such immediate symptomatic antecedents in these 26 cases are classifiable as follows: pharyngitis, tonsillitis, bronchitis, and "grippal" onset in 13 patients, dental extraction onset in five patients, gall-bladder colic onset in one, abdominal pain onset in one, kidney colic onset in one, postoperative (osteomyelitis) onset in one, neuritis and arthritis onset in two, carcinoma of bladder in one, migraine in three (one of whom is also included in the "grippal onset" group, and another in the abdominal pain group above).

A more fundamental adaptation of generally accepted views is involved in an interpretation of the mechanism of the known blood and bone marrow changes in agranulocytic angina if the drug-idiosyncrasy factor is to be accepted. The evidence in several "acute" cases mentioned above would necessitate the assumption of, first, an almost immediate granulocytoclastic crisis * occurring within a few hours to a few days of the first noxious dose of the drug, and second, a concomitant or subsequent bone marrow disturbance characterized by "maturation arrest" of the myeloid white cells at or below the myelocyte level and in many instances an apparently similar but less complete arrest, at the source, of lymphocyte and monocyte maturation and emigration.[11] These two assumptions may be made without great violence to our preconceptions. The most difficult piece of evidence, however, to fit into the "drug-idiosyncrasy" hypothesis would seem to be the apparently established fact (Kracke et al.) that granulocytopenia precedes all other clinical phenomena of the disease. This fact would be understandable in the case of habitual users of the drug or drugs in question and would merely necessitate the assumption of suddenly acquired idiosyncrasy, or of previously existing mild and unrecognized episodes of agranulocytosis. It is also understandable in some acute cases if one accepts the hypothesis of certain supposedly early symptoms being merely reasons for medication rather than true onset phenomena of the agranulocytic angina syndrome. But the drug idiosyncrasy hypothesis and the now orthodox

* This term is coined to convey the idea that granulocytes suddenly disappear from the peripheral blood either by rapid elimination, destruction, or retention in internal organs and vessels.

dictum that "granulocytopenia precedes clinical symptoms" would seem to clash hopelessly in the face of certain acute and relapsing cases of the disease which have been reported.[12, 13]

In these, and one of our own to be mentioned below in more detail, the neutropenia occurred out of a clear sky without drugs and with no symptoms requiring drug therapy until several days after the "agranulocytic" blood picture was established.

That the rôle of amidopyrine in the etiology of agranulocytic angina is not a simple toxicologic process is obvious, not only from the fact that probably less than one in many thousands of users is afflicted with the disease but also from such considerations as the following: (1) none of our patients with agranulocytic angina has taken an excessive quantity; (2) the records of two "allonal" suicides who lived four days and six days respectively, after taking between 30 and 50 tablets of allonal each, show essentially normal blood counts just prior to death; (3) the records of four private patients known for many years as habitual users of allonal (averaging at least two tablets nightly for at least three years) show repeatedly normal blood counts; (4) the records of two patients with measles and three with rheumatic fever each treated with amidopyrine in doses from 20 to 30 grains daily for from four days to three weeks show no granulocytopenia throughout.

Other drugs used by our patients, before hematologic diagnosis was established, include: aspirin, sodium salicylate, phenacetin, strychnia, phenobarbital, "amytal," sodium bromide, "salicon," "bromo-seltzer" (acetanilid), cinchophen, phenolphthalein, mineral oil, cascara, orthoiodoxybenzoate, quinine, and diphtheria antitoxin. Drugs used after diagnosis was established included many of the group just mentioned and in addition codein sulphate, morphine sulphate, digitalis, caffein-sodio-benzoate, and the usual items of treatment of the disease itself (pentose nucleotide, blood transfusions, roentgen-ray, calcium, liver extract, etc., and in two cases neoarsphenamine).

The one patient in this series concerning whom it is certain that amidopyrine could have had no connection with his repeated bouts of agranulocytic angina is a man whose wife is a physician. This patient had taken a good deal of quinine in some of his attacks of probable agranulocytic angina prior to coming under our care. The important point in this connection, however, is that since then he has had several desperate attacks of "agranulocytosis" each one coming "out of a clear sky" without any medication of any kind (not even mineral oil which our records show to be a most frequent concomitant—though assuredly a blameless one).

This series, like others recently reported, shows a high incidence of patients closely related to practitioners of medicine: one dentist's daughter, one registered nurse, one pupil-nurse, one doctor's mother, one doctor's father-in-law, one dentist, one doctor's husband, two cousins of doctors, one doctor's wife.

Six of the 26 patients gave histories indicative of definite allergy: three with migraine associated with urticaria or eczema or vasomotor rhinitis, one with asthma, and two with food sensitizations. Two of these allergic individuals and three others (not obviously allergic) gave histories suggestive of drug idiosyncrasy (e.g., "stimulation" from morphine, "weak feelings" from aspirin, "elation and vertigo" from allonal, "depression" from phenobarbital). Skin sensitization surveys made in five cases showed only a few minor food reactions. Blood calcium studies in two patients during and after attacks of agranulocytosis showed no significant abnormalities. "Patch tests" with amidopyrine, acetanilid, acetylsalicylic acid, phenacetin, phenobarbital and morphine sulphate in one recently recovered patient (who had used pyramidon, bromo-seltzer and "empirin compound" for migraine prior to onset of agranulocytic angina) were all absolutely negative (Dr. R. A. Kern). "Patch test" with amidopyrine in the most recent case—that of the pupil-nurse—was also negative.

It is clear that there are no valid tests or clinical guides to warn against the possibly noxious drugs in this agranulocytic type of idiosyncrasy, until the disease has already developed. It is then, unfortunately, sometimes too late—as evidenced by the fact that at least three patients, known to have taken amidopyrine prior to onset, and five, in whom there was no such evidence, died of the disease in spite of subsequent rigid proscribing of this and related drugs. The ordinary history of drug idiosyncrasy is untrustworthy at best and is often lacking in these cases. A clinical history of allergy, while possibly significant, is not obtainable in many patients with agranulocytic angina. Better methods of skin testing with drugs may eventually prove helpful but the evidence is not encouraging.

It is thus obvious that some presumptive evidence has been adduced in support of the thesis that amidopyrine idiosyncrasy may be an important cause of agranulocytic angina, but equally obvious that it is not the only cause. Kracke's findings would tend to incriminate any or all of his so-called "benzamine" group.[9] In addition certain of the "heavy metals" have been suspected (especially gold). One case is now on record following dinitrophenol administered for "reducing" purposes.[7] One of our cases developed during "oxoate" therapy. Several have been observed after intravenous typhoid vaccine injections and several after quinine administration (including one in this series). On the other hand the barbiturate group, at first suspected along with amidopyrine, has more recently been, at least in part, exonerated.[14, 15, 16]

An analogous problem is raised in the recent report of thrombocytopenic purpura ascribed to "sedormid" medication in one instance[17] and to "quinine and ergot allergy" in another.[18]

Closely related to amidopyrine is phenylhydrazine with its well known hematologic activity. We have never observed severe neutropenia, however, in the course of polycythemia vera under treatment with this drug. Other substances quite similar in chemical structure to amidopyrine and

phenylhydrazine are included in Kracke's "benzamine group." Each of these has from time to time in the past been observed to produce abnormal hematologic conditions other than granulocytopenia.[19]

Personal records of blood counts obtained during certain ordinary acute drug idiosyncrasy reactions (one morphine-hyperemesis, several varieties of skin rash from iodide, arsphenamine, phenolphthalein, luminal, bromide and phenylhydrazine, two cases of salicylate and quinine tinnitus and one of belladonna sensitivity) show no instance of severe granulocytopenia comparable to true agranulocytic angina. The same remarks apply to the leukocyte response in the more usual acute and chronic clinical allergies (bronchial asthma, hay fever, etc.). Occasionally, however, severe neutropenia is found in acute serum sickness and in the early phase of protein shock. It is also a nearly constant phenomenon of experimental acute anaphylactic shock (dog and guinea pig).

Conclusions

1. Our evidence suggests that amidopyrine idiosyncrasy may be a contributing "cause" of more than half the cases of agranulocytic angina. In this series of 26 patients, 17 are known to have ingested amidopyrine just before and/or during the disease.

2. A few well established negative instances, however, prove that amidopyrine cannot be accepted as the sole cause.

3. Some of these non-amidopyrine cases may possibly be caused by idiosyncrasy to other drugs and substances (quinine, dinitrophenol, orthoiodoxybenzoate, neoarsphenamine, bacterial vaccine, etc.) or to a similar abnormal reaction ("anaphylactoid") to foods, exogenous or endogenous "toxins" whether chemical or bacterial, or to hormonal substances or a "conditioned deficiency."

4. If the causal mechanism be of idiosyncratic or allergic nature, it must represent a very special blood and bone marrow sequence of events hitherto unrecognized and different from the ordinary clinical and hematologic phenomena usually ascribed to such mechanism. From the standpoint of leukocyte behavior the mechanism seems to be more like that of acute anaphylactic shock in laboratory animals than human allergy.

5. The therapeutic implications of these findings suggest the advisability of more specific attempts at "elimination" and "detoxification" especially with regard to the liver [20] as a possible seat of allergic disturbances.

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DIAPHRAGMATIC HERNIA *

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An increased interest in diaphragmatic hernia has been stimulated by its growing incidence, by the sharp difference of opinion as to what constitutes one type of herniation at the esophageal hiatus, and by the marked recent increasing measure of success of its surgical treatment.

Diaphragmatic hernia is a protrusion of abdominal viscera through an anatomically weak area or through an abnormal opening or weak area in the diaphragm, the result of imperfect development, anatomical weakness or of trauma. A sac is a component part of a typical hernia, but the great majority of hernias through the diaphragm have no sac. By common usage they are classed as false diaphragmatic hernias.

The diaphragm is a thin, fibromuscular septum between the thoracic and the abdominal cavity. It consists of a peripheral muscular, and a central tendinous portion, and has three large openings, the esophageal, the aortic and the caval. The esophageal is the only one of the three through which hernias occur. It lies at the level of the tenth dorsal vertebra a little to the left of the midline, is oval in shape and is bounded by two muscle bundles from the crurae which rise on either side of the bodies of the upper lumbar vertebrae. The inner halves of these bundles cross one another between the aorta and the esophagus, and then pass to the central tendon. The size of the muscular ring so formed varies somewhat. Hernias occur in the gap bridged by pleura and peritoneum between it and the contained esophagus.

There are two triangular parasternal areas anteriorly, between the attachment of the muscle to the xiphoid and to the cartilages of the seventh ribs where there is a gap in the muscle bridged over by peritoneum (the foramina of Morgagni), through which diaphragmatic hernias occasionally occur.

There are two triangular lumbocostal areas between the attachment of the muscle to the vertebra and the twelfth rib, similarly lacking in muscle and through which a congenital hernia may develop (the foramina of Bochdaleki). After birth these areas are protected from pressure by the upper poles of the kidneys and are therefore seldom the sites of an acquired hernia.

Abnormal openings or weak areas may be the result of incomplete or imperfect embryonic development of the structures dividing the single U-shaped celom into pleural, pericardial and peritoneal cavities. This is a complex process beginning in the human embryo 2.1 mm. long. It is brought about through the fusion of several component parts as follows:

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(1) The dorsal mesentery; (2) the septum transversum, situated anterolaterally and ventrally; (3) the pleuro-peritoneal membranes, dorsolaterally; and (4) narrow shelves, peripherally, joining the parts from the pleuro-peritoneal membranes to the chest wall.

These structures complete the division of the celom in the embryo of 18 to 20 mm. The muscular component between the pleura and peritoneum is of later, entirely independent origin. The muscle in the central portion at a still later period is replaced by the central tendinous structure. Failure of development of any part of one or more of these formative structures or failure of union of their adjacent parts results in a gap in the partition through which abdominal contents may later protrude into the pleural cavity without carrying before them any membrane or sac.

Absence of the muscular component at any point results in a weak area through which a hernial protrusion into the pleural cavity may develop. If the pleura and peritoneum representing the earlier embryonic structures are present they will form a sac for such a hernia. Similarly a hernia through the esophageal hiatus and at the foramina of Morgagni will have a sac.

Other embryological factors which may contribute to hernia formation are the development of the omental bursae and those factors incident to the relative sizes and changing positions of the stomach, intestines, and liver.

The omental bursae are two finger-like projections of peritoneum into the thick dorsal mesentery on either side of the foregut appearing in the embryo of 3 mm. Normally these projections become constricted off and disappear. If either of them remains open it constitutes a preformed hernia ring and sac.

The stomach originates as an enlargement of the foregut in the thorax in the embryo 11 to 12 mm. long. It migrates downward with the elongation of the esophagus and coincident descent of the septum transversum and by the time the diaphragm is complete it normally lies below it. If any portion of it fails to reach its normal position at the time of diaphragmatic closure it will remain intrathoracic. We then speak of the condition as congenitally short esophagus and of a "thoracic stomach." The degree of esophageal shortening and the consequent amount of stomach that remains above the diaphragm vary. The esophagus may be so short that the whole stomach is intrathoracic.

The liver begins as an ingrowth into the septum transversum from the foregut. The anterolateral portion of the diaphragm proper is later split off from the main liver mass of the septum transversum by infolding of the peritoneum, the falciform and coronary ligaments in the adult representing the only portions that remain united. Abnormalities in liver development or in the later normal atrophy of the left lobe may lead to imperfect development of the diaphragm (Broman). Failure of physiological umbilical herniation of the intestines, which normally begins in the embryo 11 to 12 mm. long, and which reaches its maximum in an embryo a little more than double that length, failing thereby to relieve increased

intra-abdominal pressure caused by the descent of the septum and rapidly enlarging liver within it, is said by some writers to be a factor in hernia formation.

Classification of Diaphragmatic Hernia

Diaphragmatic hernia may be classified on an etiological basis as follows:

(1). Congenital (true or false);
(2). Acquired (true or false);
(3). Traumatic (true or false).

A congenital hernia as here understood means one present at birth. The absence of a sac indicates that the hernia opening is due to the failure of development or failure of fusion of one or more of the anlagen of the diaphragm. The presence of a sac composed of pleura and peritoneum is evidence of hernia formation after the complete separation of the pleural and peritoneal cavities.

An acquired hernia signifies one that develops gradually after birth in a congenitally weak area such as at the esophageal opening or at the parasternal or the lumbocostal trigone. It is acquired in the same sense as an inguinal hernia is usually acquired through the anatomically weak inguinal ring. With a few exceptions such hernias have a sac.

A traumatic hernia is one that results from a penetrating injury to the diaphragm, as by a bullet or a shell fragment or a knife stab, or from tearing or bursting of the diaphragm from sudden violent abdominal or thoracic compression, as from a fall, blow or crushing impact; almost all such cases are without a sac. Some writers have excluded recent injuries of the diaphragm with prolapse of abdominal contents, while including those of long standing as diaphragmatic hernia. There seems to be no reasonable grounds for attempting to so distinguish between identical conditions on the basis of duration.

Clinically the differentiation of these etiological types may be difficult. A hernia due to a gap in the diaphragm or one with a sac present at birth is obviously congenital but such a hernia may remain latent for years and then it may be difficult to decide whether it is congenital or acquired. Many writers include the acquired with the congenital. In the study of combined series of cases it is therefore expedient to combine these two groups. A traumatic hernia also may remain latent even if it produces symptoms or signs and may remain unrecognized for years. As a rule, its etiology is evident.

Incidence

If the true incidence is to be deduced from the number of reported cases it is necessary that the diagnosis be certain. Up to recent years there could be no reasonable doubt as to diagnosis. Practically all the earlier reported cases were found at necropsy; a few were confirmed by operation. With the advent of roentgenography the demonstrations of herniation of various

parts of the gastrointestinal tract above the diaphragm also were unmistakable. However, during the last 10 years large series of cases have been reported of "herniation" through the hiatus of a small portion of that part of the stomach just below the terminal esophagus, the diagnosis having been based almost exclusively on a special technic for its roentgenological demonstration. The validity of this technic has been disputed by other observers.

In discussing the incidence of diaphragmatic hernia it therefore seems advisable to segregate the two groups.

The reported incidence of undoubted cases is shown in table 1.

TABLE I

Incidence of Diaphragmatic Hernia Exclusive of Large Series of Esophageal Hiatus Hernias

Author	Congenital	Acquired	Traumatic	Total	Remarks
Lacher		127	146	273	Exclusive of 6 cases of eventration.
Thoma (1882)		10	3	13	
Grosser (1900)		98	48	146	
Richards (1924)	115	18		133	
Greenwald and Steiner (1929)	60			60	Exclusive of 22 reported elsewhere.
Harrington		44	12	56	4 reported elsewhere.
Hedblom (1931)	116	133	351	600	Including 26 personal cases.
Hedblom (1934)	64	36	27	127	
		821	587	1408	

The incidence of "hernias" through the esophageal hiatus is given in table 2.

Åkerlund proposed a classification of esophageal hiatus hernias into three sub-groups: (1) those with a congenitally short esophagus producing the so-called "thoracic stomach," (2) the para-esophageal type in which the lower end of the esophagus remains fixed and variable amounts of stomach herniate through the ring along side of it, (3) those in which the lower end of the esophagus with more or less of the stomach prolapses through the opening—the "hiatus hernia" of Åkerlund.

"Thoracic stomach" is relatively rare. Only about 20 are reported. The para-esophageal, though generally accepted as a clinical and pathological entity, also seems to be relatively uncommon. The great majority of the cases reported belong to the third type. It has rarely been recognized at necropsy and has been overlooked on roentgenological examinations with

TABLE II

Incidence of Esophageal Hiatus "Hernias" Diagnosed Chiefly Roentgenologically and Largely Unconfirmed by Operation or Necropsy

Author	Year Reported	Number of Cases
Camman and Fineman	1924	17
Healy and Morrison	1925	53
Jenkinson	1925	25
Åkerlund, Ohnell and Key	1926	25
Pancoast	1926	11
Ude and Rigler	1929	19
Ritvo	1930	60
Berg	1930	60
Knothe	1932	300
Schatzki	1932	23
Velde	1932	16
Koeppen and Frank	1932	20
		629

the patient in the routine upright position. According to Åkerlund and others, who have reported large series of them, this is due to the usual spontaneous reduction of the herniated sac or its contrast media content, especially by gravity in the upright position. According to these writers its roentgenological demonstration requires that the patient be examined in the horizontal or partly inverted position and in some cases it also requires increased intra-abdominal pressure as produced by straining, by manual pressure, by constricting the abdomen, or by inflating the colon.

By such methods, Knothe, in von Bergmann's clinic, was able to demonstrate a "hiatus hernia" in 300 patients during one year, representing 8 per cent of all patients subjected to special gastrointestinal examination or such as were suspected of having a hernia. Koeppen and Frank found the condition in 20 (16.6 per cent) of 120 people, Velde in 16 (2.3 per cent); Schatzki, by inflating the colon to increase intra-abdominal pressure demonstrated the typical roentgen-ray in 23 (73.3 per cent) of 30 old people examined. It is thus evident that the proportion among different observers varies greatly.

The most direct evidence of the presence of a relaxed muscular and fibrous ring predisposing to herniation is offered by a series of observations, reported by Harrington, on 500 patients in whom the hiatus was palpated during the course of abdominal examination. He found the muscular ring snug about the esophagus in 65 per cent. In 35 per cent at least one finger could be insinuated between the muscular ring and the esophagus. In 5 per cent of this group three fingers could be inserted. All of this last group were subjected to special roentgenological examination for a hiatus hernia and "occasionally a small hernia was demonstrated."

The unprecedented number of cases reported by a few observers, many found in apparently normal individuals, the rarity of the condition in routine postmortem examinations, and the absence of confirmation of the roent-

genological diagnosis at operation or postmortem, except in a very few instances,* has naturally raised the question as to the validity of the roentgenological criteria on which the diagnosis of the hiatus hernia is based. According to Knothe these are (1) the recognition of the typical striations produced by gastric mucosa above the level of the diaphragm, (2) the constriction marking the border line between the stomach and esophagus lying above the diaphragm, (3) the shortening of the sub-diaphragmatic portion of the stomach, (4) the upper part of the stomach is displaced, the fornix disappearing, (5) the esophagus appears relaxed.

Some have interpreted the shadows in question as a normal dilation of the lower esophagus, denying that the folds are sufficiently distinctive to warrant the assumption that they are gastric. Others hold that there may be a shortening of the esophagus during swallowing with a consequent luxation of the part of the stomach just below the hiatus, but that the diaphragm in the immediate vicinity is also lifted into the form of a cone so that while a part of the stomach is lifted above the general level of the diaphragm, it still lies below the cone shaped part. As a result of further roentgenological, clinical, anatomical and pathological studies by Berg, Herrenheiser, Koppstein, Schatzki, Bergmann, Sauerbruch and his coworkers, Stadtsmuller and Creberg, Anders and Bahrmann and others a difference of opinion is evident as to the limits of the anatomical variation about the hiatus and as to the part that the physiological swallowing reflex plays in the production of the changes in shape and position of contrast media in the lower esophagus as observed under the fluoroscope. There is also a difference of opinion as to the significance of the changes produced by inspiration and expiration on the bolus of contrast media at the hiatus and as to whether or not the large striations seen in the roentgen-ray and characteristic of gastric wall are always a reliable criterion. Whether or not, under the various conditions of observation, there does exist an actual herniation of a small portion of the stomach through the hiatus, it seems pretty certain that such a hernia if present assumes practical importance only when it produces definite symptoms. In a great majority of cases any symptoms that may be present are mild and not with certainty referable to the condition.

Location of the Hernia Opening

The location of the hernia opening was specifically mentioned in 728 of the collected cases of Lacher, Grosser, Richards, Greenewald and Steiner, and the author. In more than 78 per cent of the non-traumatic cases it was on the left side. Of this group more than one-quarter were at the esophageal hiatus, about the same proportion posteriorly and about one-sixth were central. Of the 22 per cent on the right side, about one-quarter were centrally situated, about one-quarter were posterior and nearly one-third at the parasternal foramen.

* Akerlund reports eight of his original series confirmed later by necropsy.

Of the traumatic hernias, about 95 per cent were on the left side, nearly one-half were lateral and nearly one-quarter central; half of those on the right side were central.

Half of the bilateral hernias were at the parasternal opening. So-called bilateral esophageal hernias usually involve a bilateral distribution of the sac through a common opening.

Hernias at the parasternal opening are of special importance from the standpoint of surgical treatment. Those with a sac through the foramen of Bochdaleki are uncommon. A sac was present in only four of 60 children and in six of 19 adults in whose cases its presence or absence was mentioned. Those posteriorly situated without a sac are due to failure of closure of the pleuroperitoneal membranes and so are present before the development of the foramen of Bochdaleki. They are therefore not through this foramen.

About one-quarter of the non-traumatic hernias situated centrally had a sac indicating a faulty development either of muscle or of later tendon formation in this region, rather than a failure of closure or union of the anlagen of the diaphragm. The instances of subtotal or total absence of the diaphragm were mostly necropsy findings in infants. A small proportion survive to adult age.

The hernia contents may be a single abdominal viscus or may include any or all the abdominal organs except those in the pelvis. In a series of 857 cases there were 72 different combinations of herniation of the stomach, intestines, colon, omentum, spleen, liver, pancreas and kidney. The stomach alone was herniated in 160 cases (20.0 per cent); the colon alone in 86 (10.3 per cent); the omentum alone in 65 (9.5 per cent); the liver alone in 14, and the spleen alone in two.

A typical esophageal hiatus hernia contains usually the cardiac portion of the stomach; one at the parasternal foramen a loop of transverse colon. In a right sided hernia, except those at the esophageal hiatus and parasternal foramen, the hernia content is usually some portion of the liver.

Etiology

There seems to be no sex predisposition to congenital hernia. In a series of 124 infants, the sex distribution was equal. There is a preponderance of females with acquired hernia at the esophageal hiatus; nine-tenths of traumatic hernias are in males.

There is a marked difference in age incidence of the different types. Of the congenital hernias included in a series of 743 cases about one-third died before reaching one month of age. The great majority of patients with acquired hernias are past middle age, when the hernia is recognized. More than two-thirds of the patients with traumatic hernia are in the second, third, and fourth decades of life.

Among the congenital cases there is a frequent association of other anomalies of development, such as harelip, cleft palate, patent ductus ar-

teriosus or foramen ovale, abnormal or imperfect development of lung, liver or of mesenteric relationships, abnormal cranial development and monstrosities of various types.

The direct cause of congenital hernia openings is faulty development of the diaphragm, the specific cause of which is uncertain. It seems reasonable to believe that any one or more of a number of factors involved in the growth and shifting relationships of the anlagen of the diaphragm and of the adjacent organs may contribute to its imperfect or incomplete formation, but the frequent coexistent anomalous development elsewhere suggests the presence of a more general cause.

The most manifest direct cause of hernia formation through the esophageal hiatus, the parasternal foramen and through other areas deficient in muscular support is probably increased intra-abdominal pressure, such as that due to straining at stool, or during micturition, coughing, vomiting, labor, or due to a sudden muscular straining or sudden wrench. Mechanical factors that increase intra-abdominal pressure such as pregnancy, kyphosis, megacolon, have been repeatedly observed in relation to hernias of this type.

Weakening of the diaphragm muscle and absorption of fatty deposit between the serous membranes (in esophageal hernia) are believed to contribute to hernia formation especially in women.

Traumatic lesions may be due to penetrating injuries or blunt trauma. In a series of 318 civilian traumatic cases 165 (52 per cent) were due to penetrating injuries and 153 (48 per cent) to blunt trauma. Of the penetrating injuries 116 (20.3 per cent) were stab wounds, 35 (21.3 per cent) gunshot wounds and eight followed operation for empyema, at least some of which were probably due to operative injury to the diaphragm. Two cases were associated with fractured ribs. Of the non-penetrating injuries 66 (36.6 per cent) were due to falls, 35 (22.8 per cent) to crushing impact, 15 (10 per cent) injuries of the "jack knifing" type by falling weights. In 16 instances some type of violent strain was given as the cause.

In a series of 127 hernias due to war injuries, 44 were due to bullets, 32 to shell fragments and two to bayonets. In 49 the cause was not stated.

Symptoms

There is no entirely characteristic symptom or syndrome. There is a great variation in the symptoms produced by the same type, as well as by different types of hernia. Age incidence, pathogenesis and pathological anatomy determine certain group characteristics, but a hernia of any type may remain symptomless, being discovered at operation for other conditions or at necropsy. The first symptoms in a hernia of years' duration may be those of an acute obstruction.

Symptoms caused by the hernia are often misinterpreted, and the patient treated on the basis of a false diagnosis. The importance of familiarity with the varied clinical manifestations lies not so much in that it will lead

to a diagnosis independently as in that it will suggest the necessary further study to establish the diagnosis.

The symptoms naturally group themselves into those referable to the thorax and to the abdomen, respectively. The size and position of the hernia contents determine in large measure the thoracic symptoms, and the hernia content and differing degree of hernia ring constriction account largely for the wide range of abdominal symptoms.

Dyspnea, cyanosis, palpitation and a feeling of fullness or of suffocation, dysphagia, pain under the sternum and in the shoulder, and coughing are the most common thoracic symptoms. Hiccough is occasionally present. Dyspnea, palpitation and a feeling of fullness occur most characteristically after heavy meals or after drinking a large amount of fluid. Many patients are unable to lie down immediately after meals on account of such symptoms. Some induce vomiting or pass a stomach tube on themselves for relief of this distress. Some patients speak of a subjective feeling of the presence of fluid, of gurgling or of splashing in the thorax, others of a sense of impending disaster in connection with a feeling of suffocation. Some patients have more difficulty swallowing liquid than solid food.

The most characteristic abdominal symptoms are those of indigestion of a character more or less suggestive of peptic ulcer or of gall-bladder disease. Nausea and vomiting are common, hemoptysis and melena occasional.

Certain types of hernia have fairly characteristic symptoms. An acquired hernia at the esophageal hiatus usually produces only mild symptoms of indigestion, or more or less dysphagia, but there may be a variety of symptoms of severe grade, including such as are very suggestive of angina pectoris.

Hernias of the parasternal opening containing most often a loop of colon are characterized by constipation and colicky pains. If the loop of herniated bowel is large there may be dyspnea, a sense of suffocation and palpitation.

The immediate symptoms of a traumatic hernia may be due to the injury as such—shock, hemorrhage, pneumothorax. The later symptoms are determined largely by the size, shape and position of the hernia opening and by its content.

Symptoms of obstruction when present are similar to those due to other causes, but an associated dextrocardia and retracted abdomen are almost diagnostic of diaphragmatic hernia as cause of the obstruction.

Physical Findings

The physical changes produced by diaphragmatic hernia are chiefly thoracic and due to the pressure of the abdominal viscera in the thorax. A bulging of the thorax and decreased respiratory excursion on the affected side, changes in the percussion note and in the auscultatory findings suggestive of pneumothorax, or of a pleurisy with or without effusion, or of

pulmonary cavitation are the most common. A variation of the physical findings, particularly those of auscultation and percussion following change in position and following the taking of fluid or food, is very suggestive of hernia. Borborygmi over the thorax is pathognomonic if eventration can be excluded. Cardiac displacement is very common. A scaphoid abdomen is occasionally observed.

Diagnosis

Before the advent of roentgenography the intravitam diagnosis of diaphragmatic hernia was rare. Bowditch in 1854 made the first diagnosis in the living. Lichtenstein in 1874 wrote that of 345 cases he had collected up to that time, only two cases had been recognized clinically, and he reported the first case diagnosed on purely objective grounds. In 1912 Giffin collected 650 cases, among which the diagnosis was made during life in only fifteen.

With the more general use and greater efficiency of roentgenological examination, an increasing proportion are diagnosed clinically but often only after the hernia has been present for many years. Of 82 cases in children collected by Greenewald and Steiner, intravitam diagnosis was made in 27, but in only six clinically; 21 were diagnosed by routine roentgenological studies; 47 were found at necropsy; four were diagnosed at operation.

Traumatic hernias are often overlooked. Of 127 soldiers wounded in the late war who were later found to have traumatic hernia, over 40 per cent had symptoms for one to 15 years before the diagnosis was made. A large number of cases are recorded of acute obstruction, years after penetrating injury or blunt trauma, found at operation or necropsy to be due to diaphragmatic hernia.

Symptoms and signs as described, referable to the thorax and abdomen, not accounted for on other grounds, especially with a history of trauma of severe grade or in the presence of scars of a penetrating injury of the lower thorax, should always suggest the possibility of diaphragmatic hernia.

Roentgenological Diagnosis

Positive diagnosis usually rests on the roentgenological findings. The ordinary fluoroscopic or roentgenographic examination may furnish very strong evidence in the form of localized areas of rarefaction or of consolidation suggesting localized pneumothorax, pleuritis, eventration, hydropneumothorax or of multiple cavities in the lung. Positive proof usually rests on the demonstration of a portion of stomach or bowel above the diaphragm following a barium meal or enema. The conditions which simulate hernia most closely on such roentgenological examination are esophageal diverticulitis and eventration of the diaphragm.

Esophageal diverticulitis is usually distinguishable by fluoroscopic demonstration of the filling of the diverticulum first, whereas in hernia of the

stomach through the esophageal hiatus the opaque medium passes through the cardia into the abdominal portion of the stomach and then into the herniated portion.

Eventration may be very hard to differentiate. It requires the demonstration of the crescentic shadow of the eventrated diaphragm above the abdominal viscera, the immobility or paradoxical respiratory movement of the affected half of the diaphragm and the identification of the gas or contrast media filled stomach under it.

Failure of demonstration of the stomach or bowel above the diaphragm does not exclude the possibility of hernia. The hernia protrusion may be spontaneously reduced at the time of the examination, or the contrast medium may fail to enter the herniated portion, or a solid viscus only (omentum, liver, spleen) may be herniated.

As stated above a herniated portion of the stomach or a small real esophageal hiatus hernia is usually spontaneously reduced when the patient assumes the upright position; and such hernias therefore are usually overlooked in routine roentgenological examinations. Spontaneous reduction may occur also in other types. Examination for diaphragmatic hernia should therefore be made in the horizontal or Trendelenberg position.

The differential diagnosis of diaphragmatic hernia involves consideration of the commoner abdominal disease conditions such as peptic ulcer with its sequelae, carcinoma of the esophagus and of the stomach, gall-bladder disease and partial or complete obstruction from any cause; and also those conditions of the thorax giving somewhat similar physical findings, such as pleuritis with or without effusion, pneumothorax, pulmonary cavitation, and angina pectoris.

Complications

The most common complications are acute intestinal obstruction and its sequelae, and acute respiratory failure. Gastric ulcer is common. Shock and hemorrhage are especially associated with the trauma causing rupture.

The transverse colon is the portion of the bowel most often strangulated from constriction in a small hernial ring. Either large or small intestine, however, may become gangrenous and perforate due to obstruction of blood supply as a result of volvulus or torsion.

Acute respiratory failure as mentioned is most common in infants with congenital hernia, but may occur in adults with hernia of any type. Many cases of sudden death from asphyxiation are recorded (Fishback, Granzow). The herniated stomach or bowel may be enormously dilated.

Treatment

The treatment of diaphragmatic hernia is surgical repair. Relative unfamiliarity with the condition, uncertainty of diagnosis, the frequent technical difficulties incident to its surgical repair and the relatively high

postoperative mortality in the past have combined to create in the medical profession an attitude of false conservatism with respect to surgical treatment. Postoperative deaths from obstruction have been unjustly attributed to the operative procedure.

The mortality in obstructed cases is about two and one-half times that of those operated upon before this complication has developed. A great many instances are recorded in the literature of persistent expectant treatment in the face of recurrent attacks of symptoms characteristic of impending obstruction, which finally developed, the patient dying from it, not infrequently after an operation performed in extremis.

Many patients are allowed to drag on indefinitely as semi-invalids, some incapacitated by nervous instability, some reduced to living skeletons from inability to swallow food or from persistent vomiting.

Indications for Operation

The indications for operation should be considered in terms of the severity and gravity of the symptoms as such and in terms of the relative danger of complications and of operation in any given case.

The possibility of saving many of the infants with congenital hernia is suggested by reported successful cases. Since 1931 there are reported nine cases of infants under one year of age operated upon for the repair of the hernia. Six (66.6 per cent) recovered; in one case the opening was too large for closure; two died, one of nine months, and one "new born." One cured case operated upon by Carylles was 13 days old; one successfully operated upon by Johnson and Bower was forty-one and a half hours old. This, it is believed, is the youngest case on record. Five cases between five and 10 years of age and one 13 years of age were cured.

Most congenital hernias in older individuals are posterior or posterolateral. The opening may be assumed to be small if only a part of one viscus is herniated. If a large portion of the abdominal viscera are herniated it still may be small, but it is likely to be relatively large. If the opening is too large for primary closure it may be closed by a muscle or fascia plastic procedure, or by preliminary thoracoplasty combined with some plastic repair.

An acquired hernia ring at the esophageal hiatus may be relatively inaccessible and the edges of the ring may be ill defined, making the closure difficult. If the hernia is small and producing no marked symptoms, operation is hardly indicated, but if relatively large or producing rather marked symptoms it should be repaired.

Acquired hernia at the parasternal opening usually produces relatively severe symptoms due to partial obstruction of the colon and to crowding of the heart and lungs. The hernia opening is quite accessible through an epigastric incision. Such a hernia should be repaired unless there are very definite contraindications to operation.

Penetrating injuries in the chest wall from the sixth interspace down should be explored for injury to the diaphragm and abdominal viscera if there is any probability of deep penetration. If symptoms persist following severe blunt trauma, and roentgenological examination shows hernia, immediate repair is advisable.

Preliminary operations include enterostomy, phrenic nerve crushing and thoracoplasty. An enterostomy may be life saving in acute obstruction, the hernia being repaired at a later date. Phrenic nerve crushing will facilitate the closure of a large hernia opening centrally or peripherally situated. In case of an esophageal hiatus hernia it is of less value and in case of a parasternal hernia it is not necessary and may be harmful in that it is impossible to determine clinically through which parasternal opening a right or left sided hernia sac protrudes.

Preliminary thoracoplasty is indicated if clinical study or exploratory operation has disclosed an opening too large for direct or plastic closure.

Among 57 cases reported during the last three years the immediate result was good in 72 per cent. There were eight deaths (14 per cent). In the author's series of 22 cases operated upon there were two operative deaths, one from infection, and one, a puny child of four and one-half years, from shock.

Summary

1. Diaphragmatic hernia may be present at birth, it may be acquired through anatomically weak areas, or it may result from direct injury to the diaphragm, or from sudden accidental greatly increased intra-abdominal pressure.

2. There is an increasing incidence of reported cases, particularly of those of the acquired type at the esophageal hiatus and of those incident to wounds and automobile accidents. The greatest increase in incidence is that of the small so-called reducible hiatus hernias demonstrable only by special technic of roentgenological examination, and the inclusion of which as diaphragmatic hernia is challenged by many observers.

3. The exact etiology of the congenital type is not known; that of the acquired type is chiefly increased intra-abdominal pressure in the presence of a congenitally weak area of the diaphragm or an acquired weakness due to atrophy of muscle and absorption of fat deposit in the anatomical foramina.

4. The symptoms are referable to the thorax or abdomen or both in varying proportions and degree. The thoracic symptoms are due largely to interference with the functions of respiration or circulation or both. Abdominal symptoms are largely attributable to a greater or lesser degree of obstruction of stomach or bowel.

5. The physical findings are chiefly thoracic and due to the presence of the herniated viscera. Borborygmi, partial dextrocardia and variable physical findings, especially with changes in position, are particularly significant.

6. The diagnosis is confirmed by the demonstration of an abdominal viscus above the diaphragm. A gas filled viscus may be recognizable; one containing a contrast medium, except in case of a hiatus hernia, is unmistakable. Failure to demonstrate a hernia does not exclude it.

7. Small, reducible, symptomless hernias at the esophageal hiatus should be treated expectantly. The treatment of all other types is surgical repair unless contraindications are present outweighing the indications for operation in the individual case.

8. Intestinal obstruction is the most serious complication and operation in its presence more than doubles the operative mortality.

9. Among 57 cases operated upon, reported during the last three years, there were eight deaths, a mortality of 14 per cent.

10. In the author's series of 22 cases operated upon there were two operative deaths, one from infection, and one, a puny child of four and a half years, from shock.

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THE "Q" DEFLECTION IN NORMAL AND ABNORMAL HUMAN ELECTROCARDIOGRAMS*

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SINCE Pardee,[1] in 1930, re-directed attention to the Q-wave and reported a relative frequency of large Q_3's, in cases that showed coronary artery disease, there has been an increased effort directed toward the determination of the significance of Q and, more particularly, of a large Q_3. All such work in the Q-wave has been based on the assumption that the term Q, or Q_3, designates a more or less definite part of the electrocardiogram, and that it probably refers to the activation of a fairly definite part of the heart. In this paper we shall attempt an analysis of the Q-wave in normal records and in records of the large Q_3 type that will indicate the relative time occupied by Q. We feel that this time data throws light on the significance of the large Q-wave.

METHOD

For the identification of the parts of the ventriculogram in the three standard leads that correspond in time we have made use of Einthoven's formula as follows: when on any and every vertical line the electrocardiographic curve can be superimposed so that the height in Lead I added to that in Lead III gives the height in Lead II, the time relations are identical.

In all electrocardiograms studied we measured the size of positive deflections from the top of the base line and that of negative deflections from the bottom of the base line. When the figure for Q_1 algebraically added to that for Q_3, gave, with reasonable accuracy, the height of Q_2, it was assumed that Q_1, Q_2 and Q_3 occupied the same time interval. When the size of Q_2 differed grossly from the algebraic total of Q_1 and Q_3 it was assumed that Q_1, Q_2 and Q_3 did *not* occupy the same time interval. Similar calculations were used for R and S. When Einthoven's equation did not balance for one wave, e.g., Q_1 plus Q_3 greater than Q_2, while the algebraic total of *all* deflections in Lead I added to the algebraic total in Lead III gave the total in Lead II $((Q_1 \div Q_3) \div (R_1 \div R_3) \div (S_1 \div S_3) = (Q_2 \div R_2 \div S_2))$, it was concluded that summation had taken place so that one wave corresponded to either more or less of the time part occupied by the wave of the same name in another lead—Q_3 for example, corresponding in time to Q_1 plus part of R_1.

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The method outlined above enables one to identify peaks that coincide in time in the three standard leads of an electrocardiogram, and, when they do not coincide, to find the points in the other two leads that do correspond in time with a given peak. In figure *2A,* for example, the peak of Q_3 corresponds in time with R_1 and we, therefore, conclude that Q_3 and R_1 represent the same moment and the same process in the heart.

Normal Electrocardiograms

We analyzed electrocardiographic tracings taken from 28 student nurses at the Jewish Hospital in whom there was no clinical evidence and no history to suggest the possibility of heart disease. Three of these records showed a deviation of the main axis to the left, including one large Q_3 and one small Q_3. Twenty-five of these records showed a normal axis deviation. The Q, R and S waves appeared to occupy the same time interval in 14 of the group of 25 (56 per cent). (Table 1.) In the other nine cases Q_1 plus Q_3

Table I

Normal Records in Which $Q_1 + Q_3 = Q_2$, $R_1 + R_3 = R_2$, $S_1 + S_3 = S_2$.

Record Number	"Q" Leads I	"Q" Leads II	"Q" Leads III	"R" Leads I	"R" Leads II	"R" Leads III	"S" Leads I	"S" Leads II	"S" Leads III
2	0	−0.5	−0.5	+6.5	+ 8	+ 2	0	−0.5	−0.5
4	0	−0.5	−0.5	+6	+12	+ 6	0	−0	−0
6	0	−0	−0	+2	+ 5	+ 3	0	−1	−1
10	−1	−1	−2	+7	+ 8	+ 1	−0.5	−0.5	−0
12	−0.5	−0.5	−0	+3.5	+ 9.5	+ 6	−1.0	−0.5	−0
13	0	−0.5	−0.5	+1.5	+12.5	+11	−1	−1	−0
14	0.5	−0	−0.5	+7.5	+ 9	+ 2	0	−0	−0.5
15	0	−1	−1	+3.5	+ 9.5	+ 6	−0.5	−0	−0
17	0	−0.5	−0.5	+3.5	+ 7	+ 3.5	−1.5	−1.5	−0
18	0	−0	−0	+3.5	+ 5	+ 2	0	−1.3	−1.3
20	0	−0	−0	+3	+ 4.5	+ 1	−1.5	−2	−0.5
21	−0.5	−0.5	−0	+4.5	+ 7	+ 2.5	−0.5	−0	−0
23	0	−0.5	−0.5	+3	+ 5	+ 2	−1.5	−2	−1.5
24	−0.2	−0.2	−0	+2.5	+ 8	+ 5.5	0	−0	−0

equalled Q_2 in six (table 2). In all, therefore, Q_1, Q_2 and Q_3 appeared to occupy the same time interval in 20 of 25 tracings (80 per cent). There were four records with no Q-wave. If these are omitted, Q_1, Q_2 and Q_3 appeared to agree in time in 16 of 20 tracings (80 per cent). The five cases in which Q_1 plus Q_3 did not equal Q_2 are presented in table 3. In these there appeared to be summation so that Q in one lead corresponds to Q plus part of R in another lead. Q, however, is small in all of these five curves and occupied, at most, insignificant parts of the time taken in other leads by the first part of R. *These results suggest that for practical purposes the term Q represents a definite time interval in normal electrocardiograms.* Examination of the S-wave in this series of normals revealed

TABLE II

Normal Records in Which $Q_1 + Q_3 = Q_2$ but $S_1 + S_3$ does not $= S_2$.

Record Number	"Q" Leads I	"Q" Leads II	"Q" Leads III	"R" Leads I	"R" Leads II	"R" Leads III	"S" Leads I	"S" Leads II	"S" Leads III
3	−0.5	−0.5	−0	+6	+ 7.5	+3	−1.5	−0.5	−0
11	0	−1	−1.2	+5	+10	+8	−1.2	−0	−0
16	0	−0.5	−0.5	+4	+ 9	+7	−1.5	−0	−0
22	0	−0	−0	+4	+ 7	+6	−4	−1.0	−0
9	−0.5	−1	−0.5	+6	+12	+5	−1	−0	−0
5	0	−0	−1	+6	+10	+5	−2	−2	−0.5

TABLE III

Normal Records in Which $Q_1 + Q_3$ does not $= Q_2$.

Record Number	"Q" Leads I	"Q" Leads II	"Q" Leads III	"R" Leads I	"R" Leads II	"R" Leads III	"S" Leads I	"S" Leads II	"S" Leads III
1	0	−1	−2	+6	+13	+8	0	−0	−0
19	−0	−0.5	−1.5	+3	+11	+8.5	−0.5	−0	−0
25	−2	−1	+0	+8	+ 9	+3	0	−0	−3
7	−0.5	−0	−0	+3.5	+ 7	+3	−0.5	−0	−0
8	0	−0.5	−1	+2.5	+ 8	+8	−2	−0.5	−0

gross lack of correspondence between S_1, S_2 and S_3 in eight of 25 tracings (32 per cent). In some of these tracings S was large (up to 57 per cent of the height of the largest deflection) and could include significantly large parts of the curve that would correspond in time to R in other leads. These results indicate that S *cannot* be regarded as representative of a definite time division in normal electrocardiograms.

ELECTROCARDIOGRAMS WITH A LARGE Q_3

In an examination of 1200 consecutive electrocardiograms taken at the Jewish Hospital, 50 (4 per cent) were found which show a large Q_3 according to Pardee's criteria: i.e., Q_3 represents 25 per cent or more of the maximum deflection of Q–R–S, and there are no S_3's. Waves of the M and W types are omitted. The size of each deflection in this series is given in tables 4 and 5.

Analysis of these records in the manner in which the normal records were analyzed shows that there is no algebraic relation between the total of Q_1 and Q_3 and the height of Q_2; or between the total of R_1 and R_3 and the height of R_2; or between the total of S_1 and S_3 and the height of S_2. A relationship does appear, however, when the algebraic total of all waves in Lead I is added to that for all waves in Lead III. The grand total obtained approximates more or less closely the algebraic sum of the deflections in Lead II.

TABLE IV

Large Q_3 Series Showing Q_3's That Include Main Phase and Initial Phase

Record Number	"Q" Leads I	"Q" Leads II	"Q" Leads III	"R" Leads I	"R" Leads II	"R" Leads III	"S" Leads I	"S" Leads II	"S" Leads III
7748	−0.5	−1	−2.5	+ 8	+ 9	+ 3.5	0	−0	−0
7696	0	−2	−5.5	+10	+15	+ 6	−1.5	−0	−0
7655	0	−2	−5	+12	+13	+ 5	−1.5	−0	−0
7595	−0.5	−0.5	−2	+ 6.5	+ 6	+ 2	0	−0	−0
7521	−0.5	−0.2	−4	+ 7	+ 5	+ 3	−0.5	−0	−0
7534	0	−1	−4.2	+ 4	+ 3	+ 4	0	−0	−0
7553	0	−2.2	−5	+ 4	+ 2.5	+ 4.5	−1.5	−0	−0
7567	−0.2	−0.2	−3.4	+ 6.5	+ 6	+ 5	−3	−2	−0
7584	0	−1.5	−3	+ 3.5	+ 2	+ 3.5	−1	−0	−0
7585	0	−2	−5	+12	+14	+ 6	0	−0	−0
7489	0	−2	−7.5	+15	+13	+ 4	0	−0	−0
7500	0	−2	−7	+15	+12	+ 4.5	−1.5	−0	−0
7278	0	−1	−4	+ 7	+16.5	+16	−0.3	−0	−0
7313	0	−2	−5	+ 5	+ 3	+ 2.5	0	−0	−0
7340	−0.3	−1	−3.2	+ 6	+12	+ 7.5	−2	−0	−0
7255	0	−1	−3	+12	+ 7.5	+ 4	−4	−1	−0
7126	0	−0.3	−3	+ 7	+ 5.5	+ 2	0	−0	−0
7067	0	−0	−1.5	+ 2.5	+ 2	+ 4.6	−4	−0	−0
6962	−1	−0.5	−3	+ 6	+ 6.2	+ 5.5	−3	−0.5	−0
6967	0	−1	−3	+ 1.6	+ 4.2	+ 3.5	−4	−0	−0
6858	0	−1	−2.5	+ 7	+ 7.5	+ 2	0	−0	−0
6859	0	−3	−9.2	+10	+ 6	+ 3.4	0	−0	−0
6906	0	−1.2	−3	+ 4	+ 3	+ 2.5	−0.5	−0	−0
6716	0	−1.5	−2.5	+ 6	+ 6.5	+ 4	−1	−0	−0
6813	0	−0.2	−5	+11	+ 8	+ 2.5	0	−0	−0
6747	−0.2	−0.2	−2	+ 4	+ 3.4	+ 3	−1	−0	−0
6751	0	−0.2	−2	+ 6	+ 6	+ 3	0	−0	−0
6557	0	−0.2	−5.5	+14	+17	+ 9.5	−4	−0.2	−0
6575	0	−2	−9	+12	+15	+ 9.5	0	−0	−0
6588	−2.2	−5.4	−4.5	+ 9	+12	+ 6	0	−0	−0

TABLE V

Large Q_3 Series Showing Q_3's That Consist Almost Entirely of the Main Phase. In many $Q_3 = R_1$ and $R_3 = S_1$ in time

Record Number	"Q" Leads I	"Q" Leads II	"Q" Leads III	"R" Leads I	"R" Leads II	"R" Leads III	"S" Leads I	"S" Leads II	"S" Leads III
7713	−0.6	−0.2	−2.5	+ 6	+3.5	+1.5	−1	−0	−0
7665	0	−2	−7	+10	+4	+3	−2	−0	−0
7684	−0.2	−0.2	−3.5	+ 7	+5	+2	0	−0	−0
7634	0	−0	−2	+ 2	+2.5	+2	0	−0	−0
7586	0	−0	−4	+ 4.5	+4	+3	−0.2	−0	−0
7587	0	−0	−2.5	+ 5	+3	+2.5	−2.2	−0.5	−0
7434	−0.1	−0.1	−2	+ 5	+5	+2.5	−2.5	−1	−0
7460	0	−0	−2.2	+ 9	+5.5	+3	−2	−0	−0
7400	0	−0.1	−3.3	+ 9	+9.5	+5	−3	−0	−0
7292	−0.1	−0.3	−3.5	+ 7	+7.5	+2.5	0	−0	−0
7086	−0.2	−1.5	−3.5	+ 9.5	+8	+1	0	−0	−0
7114	−0.2	−1	−3	+ 8	+6	+1	0	−0	−0
7063	−1	−1	−5	+10	+8	+4	0	−0	−0
7064	−0.6	−0	−4.2	+ 6.5	+4	+4	−2.5	−0	−0
6865	0	−0	−4	+ 4	+2	+5.5	−4	−2	−0
6728	−0.2	−0	−2	+ 5	+3.2	+3	−0.4	−0	−0
6801	0	−0	−2.2	+ 5.2	+4	+4.2	−1	−0	−0
6816	−0.2	−2.6	−6	+ 5.5	+9	+2.2	0	−1.5	−0
6824	0	−0.5	−2	+ 6	+3.5	+4	−6	−1.2	−0
6834	0	−0	−6	+ 8	+4	+1.5	−1	−1.2	−0

It appears evident from the data given that the Q-waves in the three leads do *not* correspond in time. In other words Q_3 in these cases is not identical in time with Q_1 and Q_2 but represents a summation of the time represented by these deflections with varying amounts of the time taken by R_1 and R_2. Thus, in 30 of the 50 records studied (60 per cent) Q_3 corresponded in time with parts of R_1 or R_2 in addition to Q_1 or Q_2 (see table 4). In 20 (40 per cent) Q_3 occupied more or less accurately the same time interval as that occupied by R_1 or R_2 (see table 5). In *none* of these electrocardiograms did Q_3 occupy the same time interval as that occupied by Q_1 and Q_2. The larger Q_3 became, the less did it agree, as far as timing was concerned, with Q_1 and Q_2 and the more with R_1 and R_2. (See figure 4.)

Figures 2 and 3 illustrate the two types of large Q_3 described above and represented in tables 4 and 5 respectively.

Discussion

The data presented indicate that the Q-wave may be a physiological entity, in the sense that it may represent a fairly definite time interval and the activation of particular parts of the ventricle, only in normal ventriculograms. In abnormal ventriculograms the Q-wave represents markedly different time parts—both in the different leads of a single electrocardiogram and in different electrocardiograms. In the light of this finding it appears to us wrong to speak of Q, or of the initial deflection of the Q–R–S complex, or even of the Q of a definite lead, such as Q_3 as representative of activity in different portions of the ventricle. Since different Q_3's can occupy grossly different time divisions of the ventriculogram they can, it seems to us, represent activity in different parts of the ventricle.

There appears to be, instead of one, three possible types of Q_3 waves, as follows:

1. Those that correspond in time with Q_1 and Q_2;
2. Those that correspond in time to Q_1 and part of R_1;
3. Those that correspond in time, more or less accurately with R_1.

A study of tables 4 and 5 in accordance with this division shows that none of the large Q_3 waves are of type 1; most are of type 2; and many are of type 3. In other words, the large Q_3 waves are not comparable with the normal Q_3 wave which belongs to the first type. Figure 1 illustrates Q_3 waves of the first type described; figure 2 illustrates the second type; and figure 3 the third type.

It appears clear that the large Q_3 wave, which corresponds with part or all of R_1, cannot be produced by the mechanism which causes the small normal Q-wave. The theories of Lewis [2] and Wilson [3] of the causation of the normal Q-wave apply at most to only part of the large Q-wave. Several authors have undertaken, nevertheless, to explain the large Q-wave

by these theories. Pardee,[1] for example, quoted Lewis'[4] concept of the normal Q-wave to support a belief that the large Q_3 represented activity in the right ventricle.

Recently Fenichel and Kugell[5] have attempted a correlation of large Q-waves with pathological observations. They assume that they are referring to a more or less definite time part when they speak of the large Q-wave and conclude that it is caused by disturbance in the intraventricular septum—chiefly in the left half, posteriorly. We have shown that a large

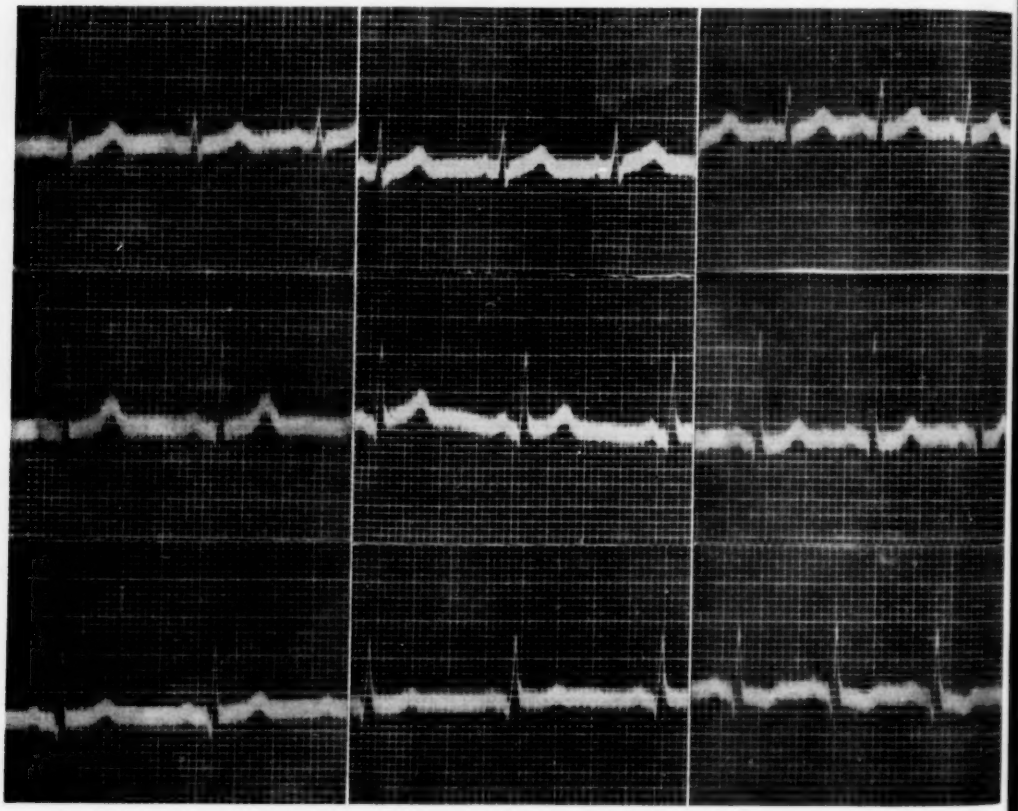


FIG. 1. Small Q_3's which correspond in time with Q_1 and Q_2.

Q_3 corresponds in time with all or part of R_1 and R_2. To accept Fenichel and Kugell's explanation of a large Q_3, one would have to conclude that R_1 and R_2 in these electrocardiograms, similarly, are, at least in part, due to septal disturbance. One would then have to explain the absence of suitable electrocardiographic representation for the rest of the ventricle. Fenichel and Kugell offer no such explanation, nor for the reduction in the size of R_3 as Q_3 gets larger, or for the usual absence of S_3 in records of the large Q_3 type. It appears to us that septal disturbances may cause changes in the initial time part of some abnormal ventriculograms, but that they

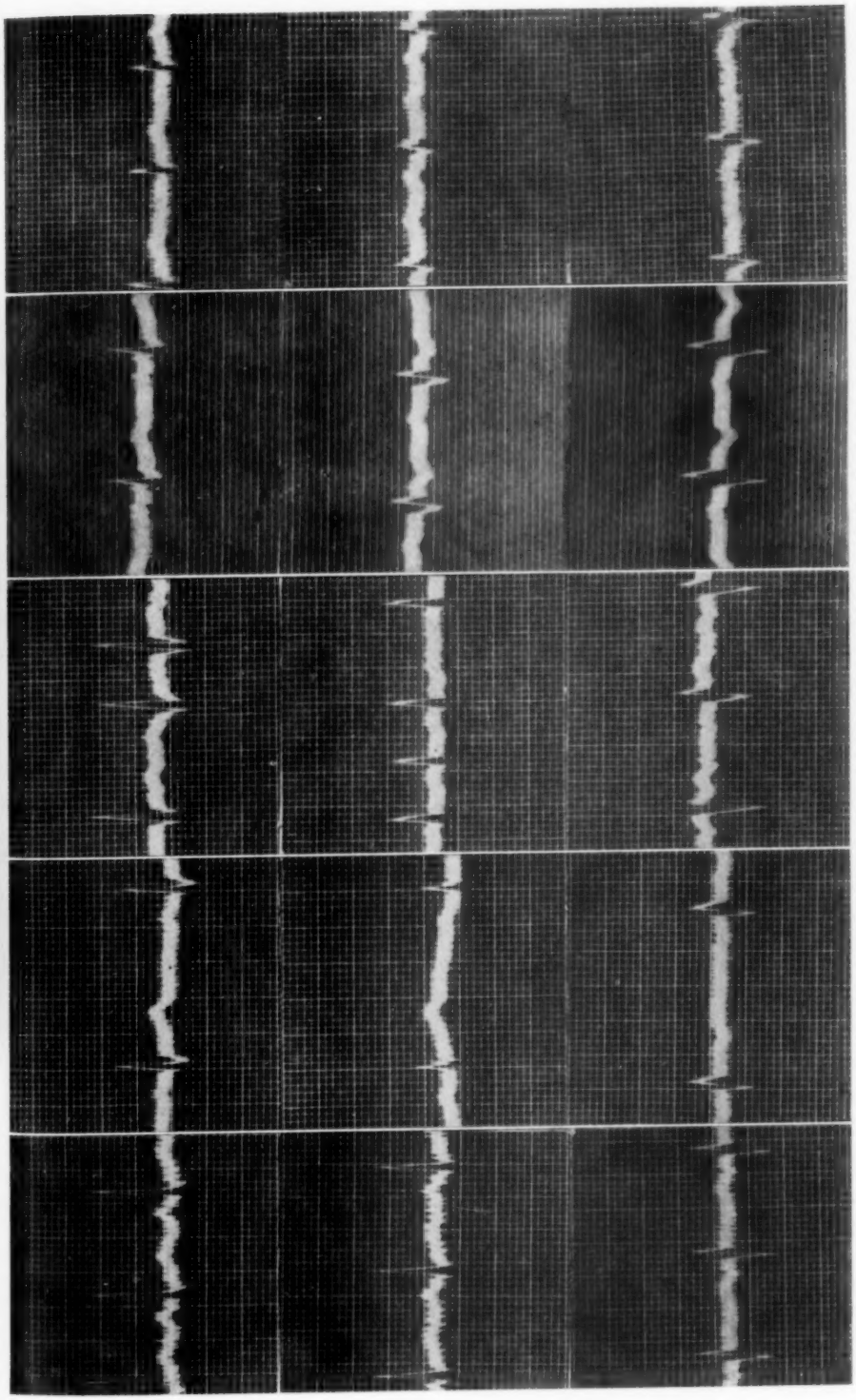


FIG. 2. Illustrating large Q_3's which correspond in time with Q_1 plus part of R_1.

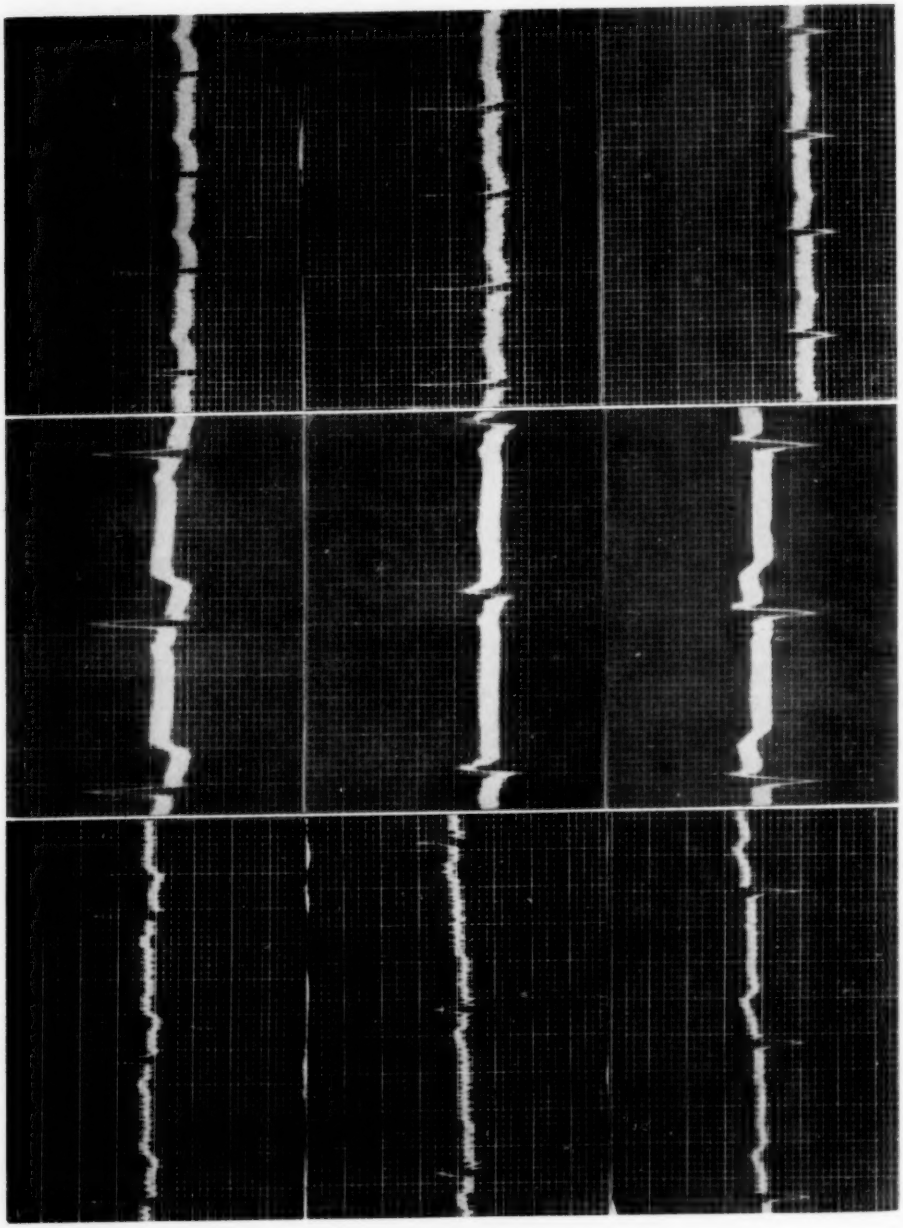


FIG. 3. Large Q_3's which correspond in time with R_3.

cannot by themselves explain those large Q_3's which represent almost all of the activation phase of the ventriculogram (figure 3). In the hearts studied by Fenichel and Kugell, pathological changes were not limited to the septum and it appears to us probable that pathologic lesions in the ventricular wall, rather than in the septum, produced most of the large Q_3 waves in their series.

We wish to emphasize at this point that in records of the large Q_3 type, the *entire* Q–R–S, not Q alone, is altered in rather a characteristic way; i.e., as Q_3 becomes larger, R_3 becomes smaller and S_3 disappears. (See figure 4.) (At times in these records P_3 becomes inverted.[15]) These facts should be borne in mind in the following discussion. They suggest a change in the spread of the excitation wave in the ventricle as a whole, rather than in a limited portion of it. Figure 4, an indifferent series of electrocardiograms with large Q_3 waves, indicates that the *larger Q_3 becomes, the smaller does R_3 become* and the more does Q_3 correspond in time with R_1. The Q/R ratio of the first electrocardiogram presented, in which Q_3 is normal, is practically the reverse of the Q/R ratio in the last electrocardiogram of figure 4, in which Q_3 is large. The fact that Pardee[1] found S_3 so infrequently associated with a large Q_3 is explainable, at least in part, by the fact that in many tracings with a large Q_3, the small R_3 present corresponds in time with S_1 and represents the same ventricular activity that S_1 represents. A study of the changes that respiration causes in the relation of the Q, R and S waves, one to another, suggests an interdependence so that when one wave varies, the others also change in characteristic fashion. (See figure 5.) The same relationship is found when a large Q is produced in pregnancy.[1, 6]

We regard as significant the work of Meek and Wilson[7] who produced a large Q_3 by rotation of a dog's heart about its longitudinal axis to the left and a large Q_1 by rotation of the heart about its longitudinal axis to the right. Their observations agree with the clinical finding of a large Q in the A–P lead in normal individuals when the right arm electrode is placed anteriorly and the left arm electrode posteriorly—an arrangement which represents a relative rotation of Lead I 90° to the left (around a longitudinal axis) or of the heart 90° to the right. (See figure 6.) As the right exploring electrode is shifted toward the left, the Q-wave becomes larger and the R relatively smaller. This is illustrated in figure 17*B* (precordial leads) of Wilson, et al.,[8] as well as in our figure 6*B*.

We believe that the assumption that a large Q is caused chiefly by rotation of the ventricular electrical axis about a longitudinal axis can explain all the known facts about a *large Q*. Such rotation could be caused:

(*a*) By mechanical factors that change the position of the heart;
(*b*) By a change in the position of the leads, causing a relative rotation of the heart;
(*c*) By damage to part of the ventricular musculature with collapse, the contraction of scar tissue or the dilatation of a damaged area;
(*d*) By thickening of one part of the ventricular musculature.

FIG. 3. Large Q_3's which correspond in time with R_1.

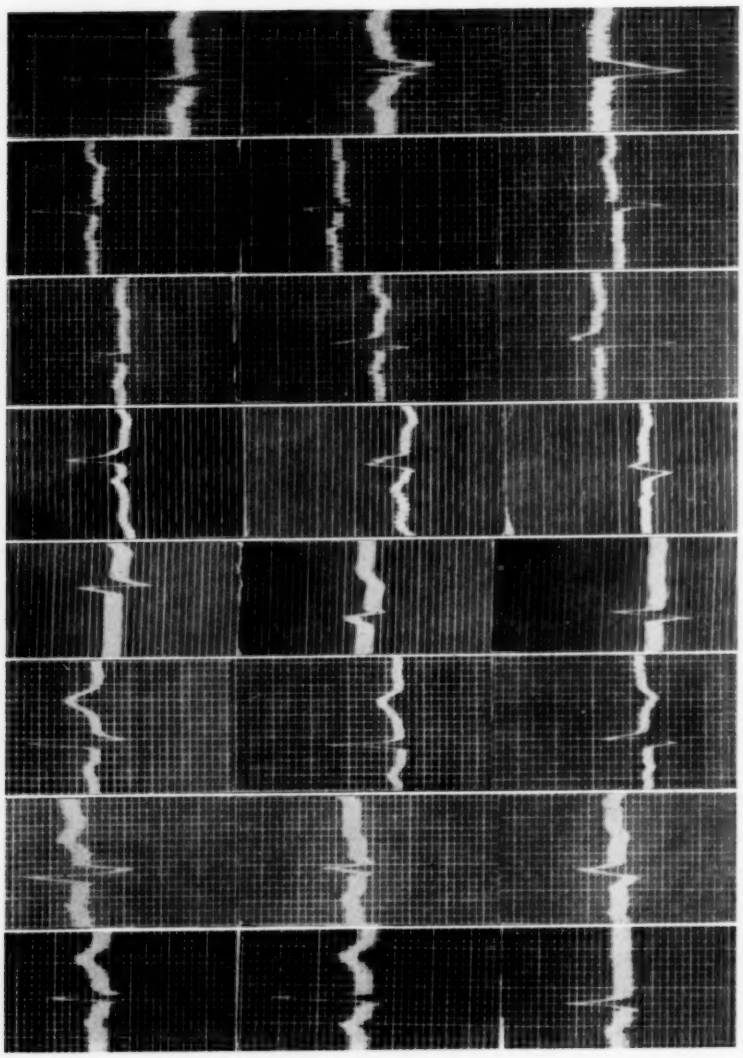


FIG. 4. Shows that as Q_3 gets larger it corresponds more with R_1 and less with Q_1. Note the occasional inversion of P_3 in these tracings.

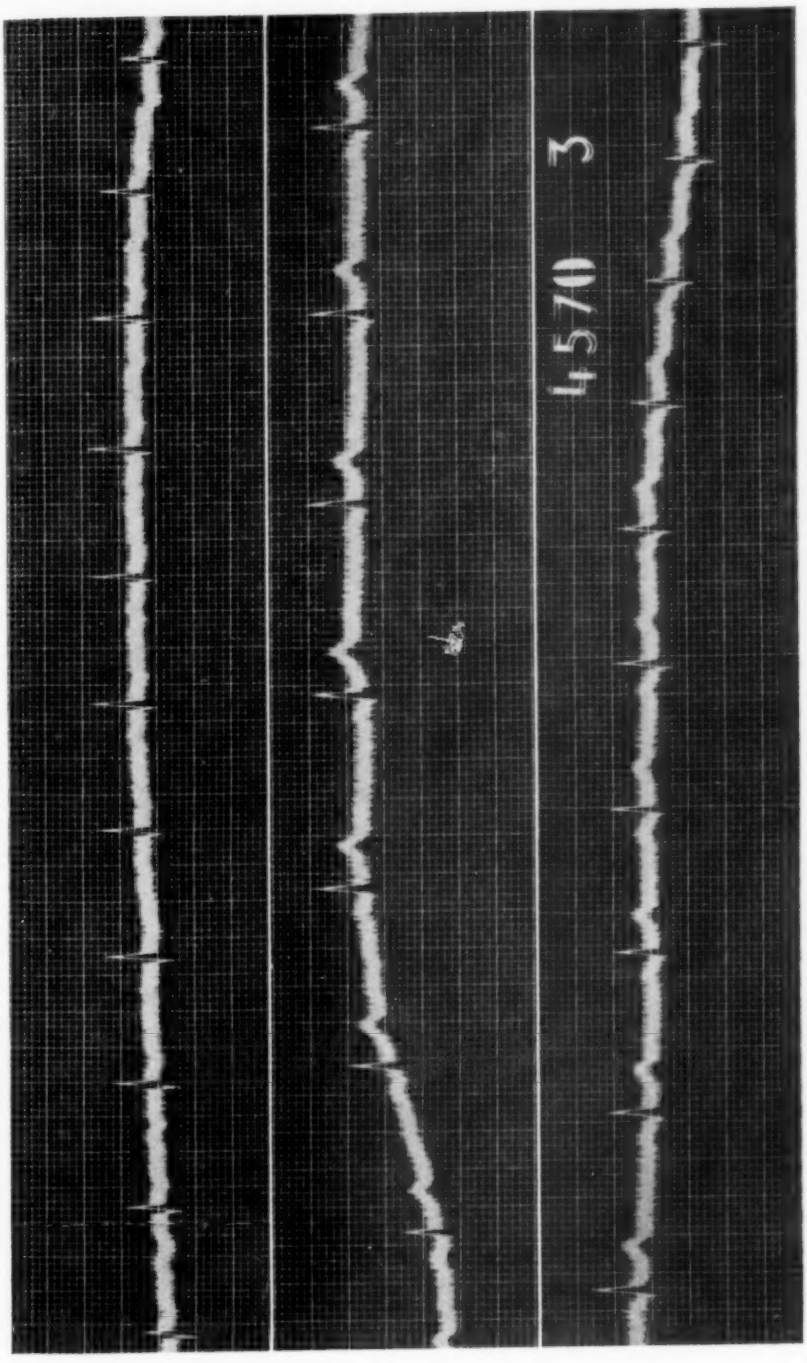
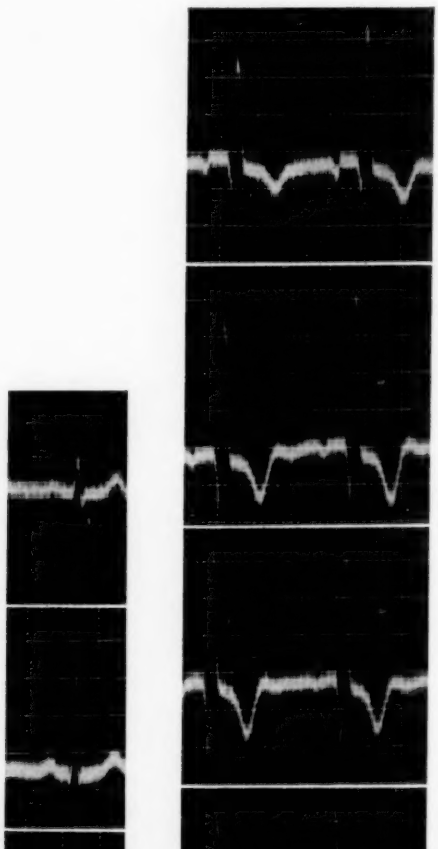


FIG. 5. This is the third lead of a curve showing the changes in the relationship of the Q and R in the respiratory phases. The three strips are continuous.

Pardee [1] and others [8, 9, 10, 11] found a large Q_3 most commonly associated with coronary artery disease—cases of hypertension, arteriosclerosis or aortitis. In this type of case the outstanding pathology consists of damage to the ventricular musculature that is more or less diffuse but is most marked



A *B*

FIG. 6. (*A*) The three conventional leads of a normal individual, from whom the posterior-anterior leads (*B*) were taken. (*B*) Anterior-posterior leads, with the left electrode placed slightly to the left of the spine, at the mid-scapula level, and the right arm electrode in 1 placed to the right of the right border of the sternum in the fourth space; 2—at the left border of the sternum; 3—at the midclavicular line, left; 4—in the anterior axillary fold at the same level. Note the increasing depth of the Q-wave and the changing relationship of the Q to the R as the exploring electrode is moved to the left, being the equivalent of an increasing rotation of the heart to the right on its longitudinal axis.

in the left ventricle—degeneration due to ischemia, or infarction with an inflammatory reaction and connective tissue replacement. It does not appear to be far fetched to postulate that collapse of necrotic heart muscle, traction due to scar tissue or dilatation of weakened areas may be causes for a relative rotation of the electrical axis about a longitudinal axis. That large Q_3's are occasionally found in normal adults, and with greater frequency in normal infants (Krumbhaar and Jenks [12] and Seham [13]), and in pregnant women [1] appears consistent with our thesis. The relative frequency of a large Q_3 in cases of pericarditis [1] is also explicable by the assumption of a longitudinal rotation of the electrical axis.

The application of this theory to the findings of Wilson and his co-workers [8] suggests that the large Q_1 found with infarction of the anterior and lateral wall of the left ventricle, secondary to occlusion of the descending branch of the left coronary artery, may be the result of a collapse of the necrotic tissue with a rotation of the electrical axis about a longitudinal axis to the right. Similarly, collapse of a dead area on the posterior wall (caused by occlusion of the circumflex branch of the left coronary artery) might produce a large Q_3 by a rotation of the electrical axis about a longitudinal axis to the left. Exceptions to the rule could be the result of dilatation of weakened areas, rather than collapse, with ensuing longitudinal rotation in the opposite direction. A clear illustration of this is given in figure 7. This figure shows a definite Q_1 T_1 group. Clinically the patient presented definite signs and roentgenologic findings of an aneurysmal dilatation of an acute myomalacia which could very well have caused a relative rotation of the left ventricle about a longitudinal axis to the right. (Shookhoff and Douglas.[14])

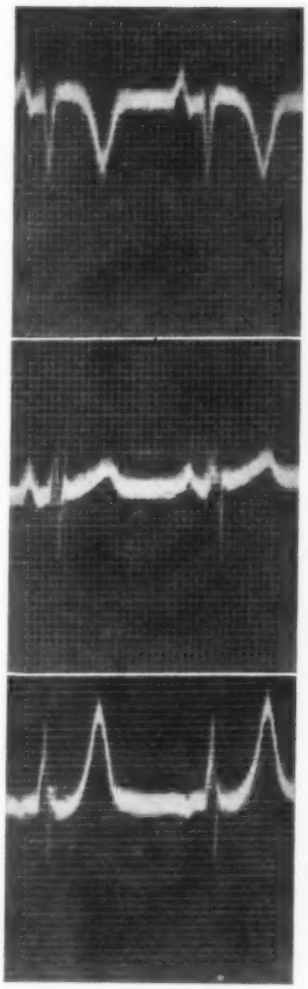


FIG. 7. A case of aneurysmal dilatation of an acute myomalacia. Note the Q_1 T_1 type of ventriculogram. Note also the inverted P_3. Taken 14 days after occlusion.

In considering the significance of a large Q_3 it is interesting to recall the history of our interpretation of a large S_3. At first the name *left ventricular hypertrophy* was given. When it was realized that a deep S_3 was not always associated with hypertrophy of the left ventricle, the name *left ventricular preponderance,* and when the inaccuracy of the latter became evident, the present name—*left axis deviation*—came into use. It has been shown that a large Q_3 may be found with normal

adult hearts, with infants' hearts, in pregnancy, and with coronary artery disease. We believe that the common factor represented is a rotation of the electrical axis about its longitudinal axis—in some cases produced by extra cardiac causes and in some cases produced by changes intrinsic in the ventricle. Other electrocardiographic changes and clinical findings must be sought as clues to the causation of any particular Q_3. (The same applies to Q_1).

Summary and Conclusions

1. In normal ventriculograms Q_1, Q_2 and Q_3 correspond in time with reasonable accuracy. In normal ventriculograms, therefore, the term "Q" represents a physiological entity and determination of its significance can be attempted.

2. In ventriculograms of the large Q_3 type, Q_3 does *not* correspond in time with Q_1 or Q_2. The time represented by Q_3 in 50 of these tracings was in *no* case identical with that occupied by Q_1 and Q_2. In *most* of these tracings part of Q_3 corresponded in time with parts of R_1 and R_2. In *many* of these tracings Q_2 corresponded more or less accurately in time with R_1 or R_2.

3. Evidence was offered to show that a large Q_3 is usually associated with characteristic changes in R and S—suggesting an alteration in the ventricle as a whole, rather than in one part of it in these cases.

4. It was suggested that a large Q might be indicative of a rotation of the ventricular electrical axis around a longitudinal axis; rotation to the left producing a large Q_3, and rotation to the right a large Q_1.

5. Such rotation could be the result: (a) of mechanical factors changing the position of the ventricle; (b) of a change in the position of the leads, causing a relative rotation of the heart; (c) of damage to one part of the ventricular musculature with collapse, the contraction of scar tissue, or dilatation of the damaged area; (d) thickening of one part of the ventricular musculature.

6. In a particular electrocardiogram there is no more reason for considering a large Q_3 indicative of coronary artery or myocardial disease than there is for regarding a deep S_3 as indicative of hypertrophy of the left ventricle. We believe that a large Q_3, like a deep S_3, is caused by a change in the relative position of ventricular musculature—for which many different causes may be responsible.

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CERTAIN BASES OF PHYSICAL THERAPY *

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DURING the past year it has fallen to my lot to become particularly interested in physical therapy. What I shall have to say is addressed not to expert physical therapists but to practicing physicians who, like myself, have had heretofore but a desultory interest in the subject and while not decrying the value of empiricism in therapeutic methods, would still wish to know something of the underlying physiological factors that may have been determined.

Although physical therapy may have been over-exploited here and there during the past several years, one gets the impression that it is much more widely neglected to the great detriment of many patients who are badly in need of it. The Council on Physical Therapy of the American Medical Association is doing a valuable work in disseminating useful information on this subject and in protecting the profession against misleading and deceptive advertising. They have wisely emphasized the point that among the physical methods of treatment the fundamentals are massage, active and passive exercise, muscle training exercises and the application of heat. As a corollary to this statement one may add that a well trained, skilful technician, intelligently directed, is of more value than much costly apparatus.

In addition to manual methods, what external stimuli do we find employed? Perhaps it will serve a unifying purpose to glance for a moment at the range of electromagnetic rays, the source of so many marvels in the physical world of today. On the left of the range are the shortest waves, the so-called cosmic rays, then successively with increasing wave lengths, the gamma rays, the x-rays, and after a relatively unknown gap the ultra-violet or chemical rays, the narrow band of visible light (from 360 to 760 millimikrons), followed by the broad band of infra-red or heat rays, the Hertzian rays that include the shorter and the longer radio waves, and finally at the extreme right of the range, the alternating current waves. You will note that many of our physical therapy modalities have their bases in electro-magnetic rays of one or another wave length, and it is safe to say that the potentialities of further discoveries in this electro-magnetic range seem infinite.

In the use of physical methods one may wish to affect many different tissues and parts of the body, but the most exposed and the most accessible of them all is the skin with its immediately subjacent tissues. We have all been taught, but we are prone to forget, that the skin is not merely an integument, a covering for the body, but a complex tissue with many func-

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934.

tions. Let us pass some of them in review. First, there is the integument, a physical barrier to the outside world. Second, the sebaceous glands. Third, the blood vessels with their remarkable reactions in maintaining and regulating body temperature and in defense against injury. Fourth, the lymph vessels. Fifth, the sweat glands with their service in temperature regulation and in excretion. Sixth, the function of insensible perspiration, also of value in temperature regulation. Seventh, the nerves and nerve endings, the sources of sensory impressions and of reflex activities. Eighth, other metabolic or chemical factors under which we may mention (a) resorption, a factor of little importance in the human skin, (b) pigment formation, (c) the histamine-like substance postulated by Lewis, (d) ergosterol, which is changed by ultra-violet irradiation to viosterol, with the production of vitamin D, (e) the high potential of tissue immunity emphasized by Kahn who finds that the skin possesses a specific reacting capacity for antigens more than ten times as great as the reaction capacities of muscle, of brain, or of plasma.

The skin then is a complex structure capable of a variety of reactions to stimuli both from without and from within. The vascular mechanisms are particularly intriguing and have been studied by many physiologists, including Sir Thomas Lewis, who found that numerous and widely different forms of stimulation yield in common three distinct events; these are (a) a primary and local dilatation of the minute vessels of the skin, (b) a widespread dilatation of the neighboring strong arterioles brought about entirely through a local nervous reflex, and (c) locally increased permeability of the vessel wall. In explanation of this complex mechanism he postulates the release of a histamine-like substance and considers it a normal metabolite that is responsible for many of the normal vascular reactions as well as those occurring under conditions of stress. In the light of such researches it seems entirely probable that many of the reactions of the skin and other tissues to physical therapeutic procedures are really defense reactions on the part of tissues to outside agencies and are non-specific as far as the particular therapeutic method is concerned. There are of course specific responses as illustrated by the difference in the skin reactions to heat rays and to ultra-violet rays, and by the striking difference in reflex activities following the applications of cold and of heat. All these responses, specific and non-specific, may be considered defense mechanisms and whenever the defense reaction is favorable to the condition under treatment, the therapeutic method is useful.

Heat

As many of the procedures in physical therapy involve the use of heat, we may well consider next some of the results of local and of general heat that have been determined by physiological experiments. Let us recall that although we customarily speak of the body temperature as 37° C. (98.6°

F.), the temperatures in different parts of the body are not the same. There are many temperature gradients that may be modified by the application of additional heat.

The heat capacity of the tissues is high (0.8) so that considerable heat may be absorbed before a change in temperature can be measured. This capacity varies also with different tissues. The conductivity of heat in the tissues is made quite variable by the marked changes in vascularity. When the skin and subcutaneous fatty tissues are cold and the vessels contracted, the conductivity is relatively poor and less heat is given off from the surface. When, on the other hand, the tissues are warm and the vascular channels dilated, the conductivity is markedly increased.

Heat may, of course, be applied by different methods, namely, by conduction as with the hot bath or a hot water bottle; by convection as from hot air; by radiation as from the sun or therapeutic lamps; and by conversion whereby electrical energy is converted into heat within the tissues of the body as by diathermy. A favorite method for superficial heating is the use of radiant energy, the most valuable wave lengths for this purpose being those of visible light and of the infra-red. The wave length with the greatest penetrating power through the tissues is given as 1150 millimikrons, that lies in the near infra-red. This wave length is best obtained by the use of a gas filled, tungsten filament bulb.

Owing to the slow penetration of heat by conduction when it is applied to the surface, to the relatively poor penetration of the infra-red rays, and to the efficiency of the local vascular protective mechanism, it is now generally believed that the use of diathermy is the method of choice in attempting to heat the deeper tissues in most conditions where this is desired. Even here, although the heat is generated within the tissues themselves, it is rapidly dissipated, no great storage of heat occurs and there is no striking rise of temperature. But after all, the chief purpose in the local use of heat in physical therapy is usually not so much the production of an increase in temperature per se as an acceleration of the circulation, an increase in blood flow, which must occur in a part where there is a large additional amount of heat to be dissipated. Hence the absence of any striking rise in temperature is not necessarily an indication that a useful purpose is not served by the treatment.

In view of the importance of an active circulation for the dissipation of heat within the tissues and for their protection from damaging degrees of heat, one must needs be careful in its application to parts where the local circulation is notably defective. Here we have an explanation of the well founded dread of heat that many physicians have in the treatment of gangrene and even of the lesser manifestations of peripheral vascular disease. This danger would seem to be obviated by the method of controlled heat suggested by Starr, who finds that the optimal temperature in such cases is usually that of the normal skin temperature of the part.

The Effect of Heat on the Circulation. This very important effect of heat is exerted both directly upon the vessel walls and reflexly through the vasomotor nerves. Heat produces vasodilatation and cold, vasoconstriction. Not only is the effect a local one but through the reflex activities distant parts of the vascular tree may be affected as has been demonstrated definitely by Lewis and others.

There are marked variations in the blood flow as the result of heat or of cold. The local circulatory rate in the arm in an arm bath has been measured and recorded. At 32° C. (approximately the normal temperature) the flow of blood was 13 c.c. per 100 c.c. of tissue per minute. At 26° C. the flow was 5.5 c.c. of blood per 100 c.c. of tissue per minute. At 46° C. the flow was 26 c.c. of blood per 100 c.c. of tissue per minute.

Heat also produces a marked increase in the transudation of fluid from the blood vessels and hence in the formation of lymph. When these vascular changes are widespread as in a warm bath, for example, there occur definite readjustments in the fluid balance with increased formation of lymph in the skin and subcutaneous tissues but, in the splanchnic area vasoconstriction, diminished capillary tension and increased absorption of water. Similarly, cold applications to the skin may result in vasodilatation of internal vascular beds and a consequent diuresis.

Effects of Heat on the Blood. When the blood is heated locally there are marked changes in its physical chemistry with a shift toward the acid side as is illustrated in the following experimental record. The blood was obtained from an arm vein after the arm had been placed in a water bath at the different temperatures. At 33° C. (91.4° F.), pH 7.45; pOH 6.3; CO_2 tension 35 mm.; O_2 saturation 70 to 90 per cent; O_2 tension 45 to 55 mm. At 40° C. (104° F.) pH 7.3 to 7.4; pOH 6.2; CO_2 tension 45 mm.; O_2 saturation 90 per cent +; O_2 tension 70 to 95 mm.

The Effect of Heat on Metabolism. The metabolism of the tissues is definitely increased by heat. As tested upon an isolated organ, as in the perfused heart, it is estimated that the metabolism increases two or three times with a rise of 10° C.

There is an interesting experiment in the study of cyanosis in the forearm produced by stasis due to a constricting band on the upper arm. In a water bath at 31° C. (87.8° F.) cyanosis was obvious in three minutes; at 42° C. (107.6° F.) cyanosis occurred in one minute; at 15° C. (59° F.) no cyanosis occurred in 15 minutes. From this experiment it is obvious that the usage of oxygen was markedly affected by the changes in temperature.

Hitherto we have been dealing with the local application of heat. As you well know, by more general heat applications or by the prevention of heat loss, a rise in the general body temperature can be induced. The complex changes that are brought about by elevating the body temperature may be summarized as follows: Increased circulatory rate, rise in blood volume, marked increase in the ventilation rate, fall in alveolar CO_2 tension,

rise in oxygen consumption, increased metabolism, and changes in the pH of the blood and urine to the alkaline side. Clinical work indicates a definite change of tone in the autonomic nervous system.

Exercise

To quote Barr: "Muscular exercise is accompanied by the coördination and integration of many functions. The participation of higher nerve centers, and the increased respiration and circulation are as much a part of exertion as the muscular contraction itself." During the contractile phase of muscular activity there is a breaking down of glycogen into lactic acid and during the recovery phase the lactic acid is re-converted into glycogen. "Due to the accumulation of acids there is during the contractile phase a diminution of alkalinity, not only in the muscles but also in the whole body, a change which is corrected during the recovery phase."

Massage

With massage, on the other hand, there are no such complicated re adjustments as in active exercise, nor do we find metabolic changes like those associated with the use of heat. There does occur, even with light stroking, a non-specific reaction on the part of the minute vessels of the skin, and with deep massage doubtless of those in the muscles also. Capillary dilatation has been observed microscopically by Pemberton and others following light massage. There is further the mechanical assistance to the venous blood flow and also the lymph flow with presumably in this way an aid in the removal of waste products from the tissues affected. Probably in this way, too, is brought about the increase in the red blood cells and hemoglobin of the circulating blood as well as the increased oxygen capacity that has been noted following massage. In spite of the paucity of physiological data there is no doubt from the empirical standpoint of the value of massage. One of the most ancient, it is also one of the most valuable measures in the realm of physical therapy. Of great value to many chronic invalids who must, for one reason or another, remain in bed for periods of weeks, it is really indispensable in the rehabilitation phase of the treatment of injuries and of many diseases of the bones, joints and muscles. Yet so great is the neglect of this useful procedure in many localities that patients must go to the osteopath or to the chiropractor in order to receive its benefits.

The Ultra-Violet Ray

The treatment of rickets, infantile tetany and osteomalacia by means of the ultra-violet ray rests upon abundant biochemical studies. It is generally agreed that the favorable effects are due to photochemical reactions resulting from absorption of the rays and the prevailing opinion at present favors the view that the sterol in the skin is rendered photoactive by radia-

tion. It has been shown that irradiated animal or human skin is antirachitic and that this action is independent of the nervous or circulatory systems.

The use of ultra-violet rays or of heliotherapy in the treatment of extrapulmonary forms of tuberculosis, of erysipelas, and other superficial infections rests chiefly upon an empirical basis.

In conclusion, in this brief and quite incomplete discussion of certain bases of physical therapy it is suggested that they are chiefly defense mechanisms of the tissues in response to external stimuli and that the most valuable of these mechanisms from the therapeutic standpoint would seem to be those of the vascular system with increased flow of blood through the part treated.

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THE DIABETIC CHILD*

ETIOLOGIC FACTORS

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Heredity

Heredity is the most important factor in the causation of diabetes in children. In a study of literature from all over the world, which includes 1,418 cases of diabetes in children, the disease was hereditary in 30.8 per cent (table 1). In reality this percentage is higher, for the longer the

Table I

Heredity in Children

Author	Number of Cases	Heredity		Familial Hereditary Per cent
		Familial Per cent	Hereditary Per cent	
Collens-Grazel	10			50.
Freise-Jahr	60	10	1.6	11.6
Holt	50			30.
John	214	4.6	14.	18.7
Joslin-White	750			40.
Lion-Moreau	100			23.
Ladd	35		37.	37.
Priesel-Wagner	108			27.
Toverud	47			17.
Smyth	31			54.
Total	1418		Average	30.8

diabetic children live the more diabetes is discovered in their families. The true percentage on this basis is probably somewhere near 40 per cent.

In my own series of 214 cases of diabetes in children and adolescents, the proportion in which heredity played a part was about equal in the boys and the girls, namely 18.7 per cent (table 2). There was an interesting contrast, however, in the hereditary factor among Gentile and Jewish children. In the Gentile children, there was a family history of diabetes in 17.9 per cent, whereas in the Jewish children it amounted to 30 per cent (table 2). Unfortunately I have no figures to offer for the incidence of childhood diabetes in the two races.

P. White in a series of 533 diabetic children, 45 of whom were Jewish, found the hereditary incidence to be 44 per cent in the Jewish group, and Priesel and Wagner in Vienna, in a series of 108 children, 29 of whom were Jewish, found 43 per cent with a familial history among the Jews, as contrasted with 21 per cent in the Gentile group (table 3).

* Read at the Chicago meeting of the American College of Physicians, April 18, 1934.

TABLE II

Heredity (John)

Total number of diabetic children 214. Boys 111, girls 103

	Familial		Hereditary		
	Number Cases	Per cent	Number Cases	Per cent	Total Per cent
Boys	5	4.5	17	15.0	19.5
Girls	5	4.8	13	12.6	17.4
Total	10	4.6	30	13.8	18.9

Relation in Heredity in the Jewish and the Gentile Children

	Familial		Hereditary		
	Number Cases	Per cent	Number Cases	Per cent	Total Per cent
20 Jewish			6	30	30
194 Gentile	5	2.5	30	15.4	17.9

TABLE III

Heredity Relation in the Jewish and the Gentile Children

		Gentile		Jewish	
Author	Total No. Cases	Number Cases	Heredity Per cent	Number Cases	Heredity Per cent
John	214	194	17.9	20	30
White	533	488	?	45	44
Priesel-Wagner	108	78	21.	30	43
Average			19.4		39

It has been pointed out by many authors that diabetes is transmitted as a recessive character according to the Mendelian law. This is shown graphically in figure 1, in which the black dots represent the diabetics, the clear rings the non-diabetics, and the half clear rings the non-diabetics with a hereditary background. The first diagram shows that when a diabetic marries a diabetic all the children will be diabetic; the second that in a union of a diabetic with a nondiabetic with a hereditary background, one-half of the children will be diabetic. The third diagram shows that when a nondiabetic with a hereditary background marries a nondiabetic of the same type, one-fourth of the children will be diabetic; and the fourth shows that when a diabetic marries a normal person with no familial-background of diabetes, no children will be diabetic.

This then gives one a practical working basis for prognosis and indicates the practical and moral responsibility which we physicians face in advising a diabetic concerning marriage. If the birth of future diabetics

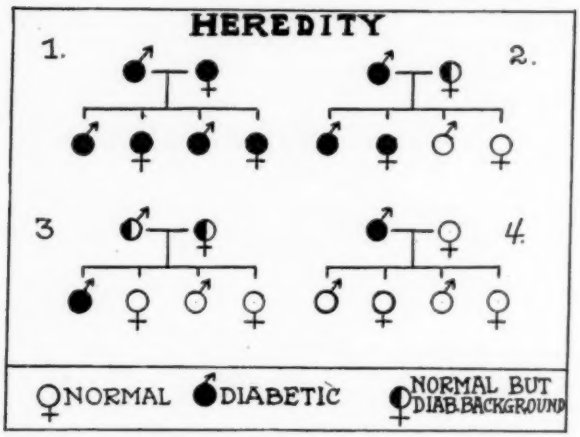

FIG. 1. Heredity in diabetes. Illustration of the Mendelian recessive.

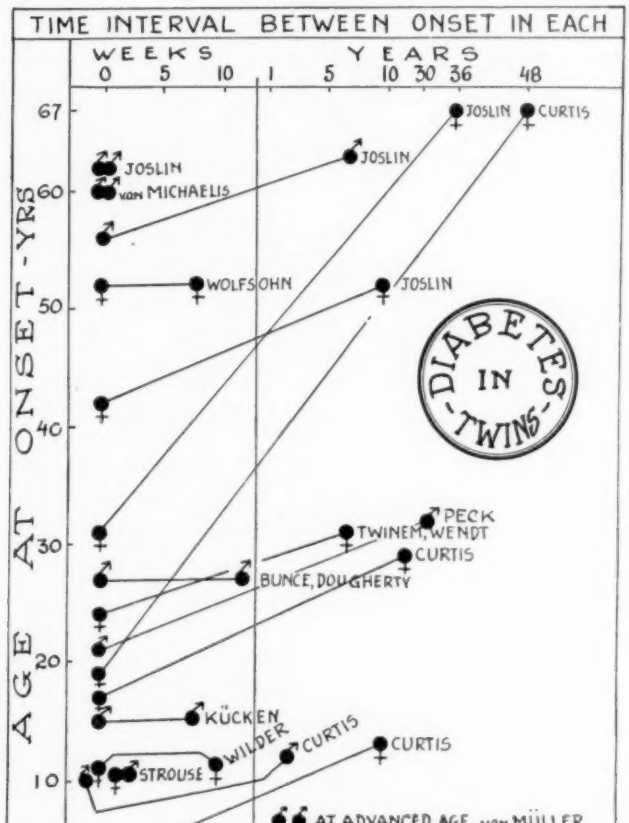

FIG. 2. Twins with diabetes. The sex, the interval of time between the onset in each pair and the author who reported them.

is to be prevented the other partner must not only be nondiabetic, but also have a family history free from diabetes.

Figure 2 presents a study of diabetic twins arranged according to the time interval between the onset of diabetes in each pair in a total of 19 pairs of twins reported in the literature. In three pairs the onset was simultaneous, and in four pairs within 12 weeks of each other. Such data present instructive and presumptive evidence of the hereditary nature of diabetes.

Infection

Infections play a considerable part in the production of diabetes in children. When one considers the havoc which an infection plays even in a mild case of diabetes, one can readily understand why an infection might precipitate diabetes in a diabetotrophic child, that is, one with a tendency toward diabetes. Figure 3 illustrates the damage caused by infection in

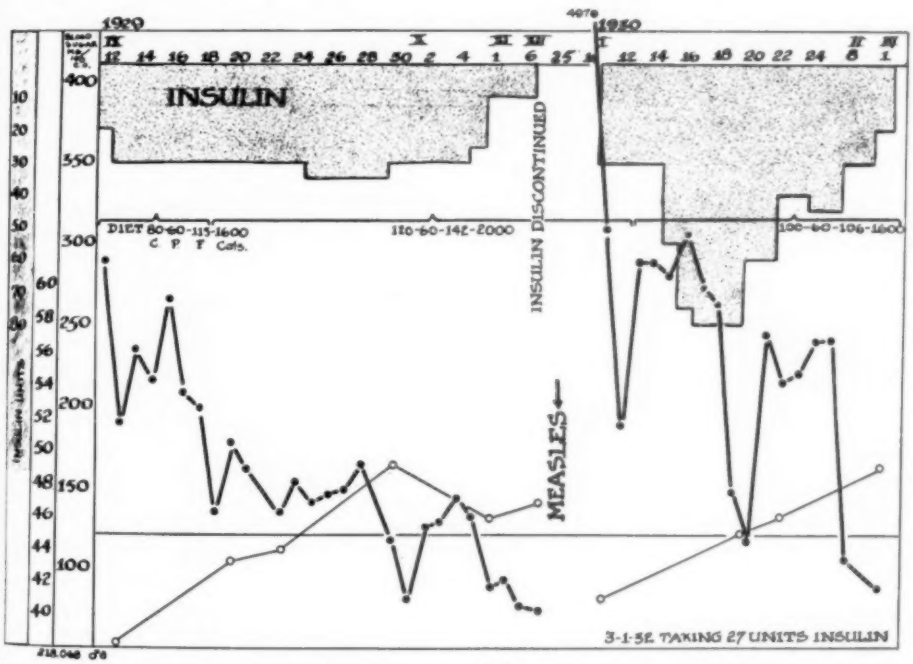

Fig. 3. Infection and the part it plays in a child who was a mild diabetic. Note the permanent loss of previous tolerance.

the case of a little boy, aged four years, whose diabetes had improved under adequate treatment so that all insulin could be discontinued. He presented a normal fasting, noon and evening blood sugar and was sugar-free on diet alone on repeated examinations. He contracted measles and, as the physician who was attending him in the small town where he lived did not appreciate the change in the situation and the need for reinstating insulin during the course of the infection, when I saw him a few weeks later his blood sugar was almost 500 mg. per cent and he displayed signs of severe

acidosis. Insulin had to be reinstated in large quantities and to this day he is taking large quantities of insulin, because the faulty management during the infection wrought permanent damage which apparently is irreversible. This case shows the importance of proper management during acute infection in a diabetic child.

There is some evidence that in all acute infections, even in normal persons, there is decreased sugar tolerance. If the reserve insulogenic function is sufficient, it is not exhausted even by repeated infections. But a lesser reserve is more easily exhausted and diabetes may be thus precipitated. Unfortunately we usually see these children at the time when diabetes develops and we know little or nothing of their background, that is, whether that child had diminished insulogenic function before the infection or whether this was normal. This phase of the problem of diabetes will have to be explored if we expect to arrive at any sort of logical solution, which will aid in the prevention of diabetes. Prevention, after all, is the only worthwhile goal, for we cannot cure diabetes, but with increased knowledge we should be able to reduce its incidence.

That infection does play a part in the development of diabetes in children can be deduced from figure 4. These data on a group of my own series

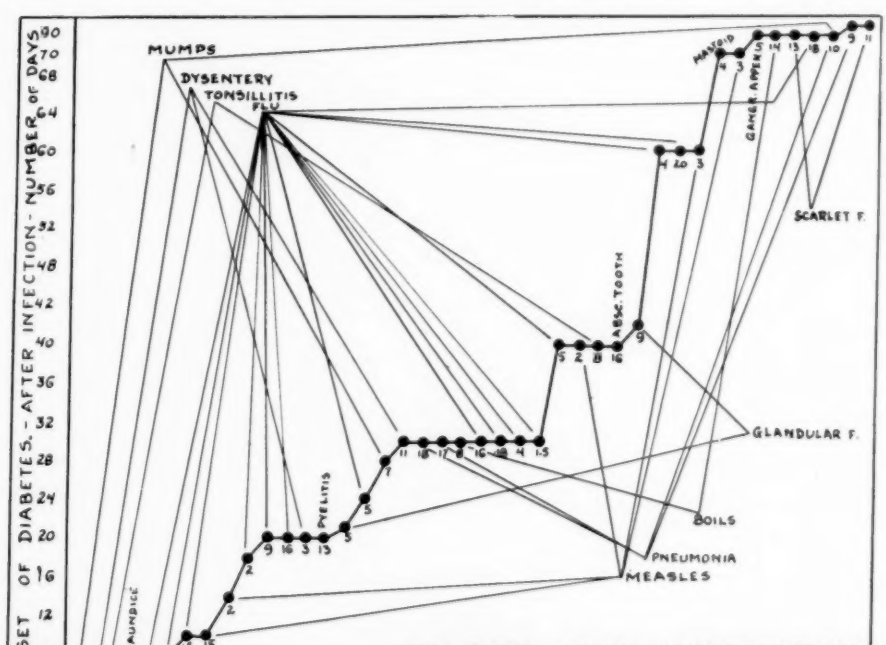

FIG. 4. The onset of diabetes in a group of 34 children from my own series following the various infections and the length of time intervening between the infection and the onset of diabetes.

of cases show the relation of the onset of diabetes to preceding infection. The time between the infection and the onset of diabetes often is very short; in some instances only two days, in nine cases 10 days and in 15 cases 20 days. Such evidence can not be disregarded. In table 4 I have gathered

TABLE IV

Onset of Diabetes in Children Following Infections

	Number of days after infection when diabetes was discovered							
	1–10	11–20	21–30	38	41	58	Not Stated	Total
Mumps	2	1	1				24	28
Influenza	4	3	5	1		2	1	16
Measles	1	1	1	1		1	1	6
Dysentery	1	1	1				3	6
Pneumonia			2				1	3
Int. toxemia							3	3
Boils	1		1					2
Tonsillitis	1			1				2
Nephritis							2	2
Glandular fever			1		1			2
Jaundice	1							1
Septic endoc.							1	1
Poliomyelitis			1					1
Abscessed teeth				1				1
Infectious diseases							23	23
Pyelitis		1						1
Total	11	7	13	4	1	3	59	98

from the literature cases of diabetes in children following an infection and have added similar cases from my own series. I do not know the background of these children, that is, whether they were perfectly normal or whether they were children with a diabetic tendency, a diminished insulogenic function, the "Minderwertigkeit" of the Germans. I suspect the latter, but I cannot be sure. Priscilla White [1] in her book on "Diabetes in Children and Adolescence" states that "infections play no rôle or are of little or no significance in the production of diabetes in children." This statement certainly is contrary to my own experience.

A. Jones [2] in England called attention to the fact that following an influenza epidemic, the incidence of diabetes increased. Lierle and Potter [3] of Iowa City, in their study of the diabetic child, state: ". . . we have observed that low grade and early diabetic conditions are recognized first during acute colds and tonsillitis." Von Noorden [4] also believes that diabetes does develop following infection. Hirschfeld [5] has expressed the view that an infection such as angina or flu causes damage to the pancreas and can bring about diabetes. Freise and Jahr [6] state that nearly three-fourths of their diabetic children developed diabetes shortly after acute infections. Similar statements have been made by von Starck,[7] Weiland,[8] et cetera.

Pancreatitis follows at times as a complication of parotitis. It is perhaps more frequent than the literature would indicate, for not all cases are reported. In 1900, Jacob [9] reported a case in a child, aged 10 years. In that same year Priestley [10] reported two cases, one in a boy aged 14 and the other in a man of 25. Auché [11] in 1905 reported two cases in boys 9 and 12 years of age. Brahdy and Scheffer,[12] Gentry,[13] Stevens [16] and others have reported additional cases. Farnam [14] collected from the literature 119 cases of pancreatitis complicating mumps and added one of her own. Barbieri [15] tells of a boy six years old with mumps during an epidemic. Six days after the onset of the symptoms he complained of a continuous pain above the umbilicus which radiated around the right side to the right lumbar region. The pain continued, next day he vomited and developed diarrhea. Two days later he had a voracious appetite and a great thirst but everything he ate he vomited an hour later. He drank two liters of water a day. The urine was loaded with sugar. The symptoms subsided gradually and disappeared after 15 days and by that time the urine was sugar-free.

That infection produces a marked rise of blood sugar even in young infants, or produces a diabetic type of curve was shown by Fritz Goetzky.[17] In an infant three and a half months old with fever and bilateral bronchopneumonia, the fasting blood sugar was 79, but after the administration of 10 gm. of glucose in tea, the blood sugar taken after three hours was still 264 mg. per cent. In another infant, two months old, with fever and hydration, the fasting blood sugar was 120 when the fever subsided on the third day, but when 12 gm. of glucose were given in tea the blood sugar rose to 178 at the end of the second hour and at the end of the fourth hour it was still 134. Lauritzen [18] recommended as a prophylactic step in diabetes the testing of children's tolerance by the production of glycosuria *ex amylo*.

MacLean and Sullivan [19] studied the tolerance of 97 children from three months to five years of age with various diseases. Seventeen infants with infections in the acute stage did not reveal any consistent change in the carbohydrate metabolism. Ten showed normal, six increased, one decreased tolerance.

This I think is quite suggestive. Out of the 17 children but one showed a decreased tolerance. Why? Was the infection due to a more toxic organism or was the infant one with a smaller insulogenic reserve? This is the type of child to follow carefully through succeeding years, for if the decreased sugar tolerance was the result of lessened insulogenic reserve this child should later in life develop diabetes. This sort of study forms the foundation on which we can build and eventually hope to reach the point of better understanding of the functional background of diabetes. It may lead nowhere and again it may shed much light on this problem.

According to Williams and Dick [20] there is a lowering of dextrose tolerance in acute infections and it may last for several months.

Labbé and Boulin [21] stress the fact that during infection glycemia is increased and the glycemic curve is four times longer, with the maximum hyperglycemia increased by 50 per cent. This reveals an important change of the sugar regulating balance. Alimentary glycosuria was noted in 75 per cent of their series. The disturbance of the glucose regulation did not parallel the gravity of the infection. The impairment of glucose balance sometimes becomes more pronounced during convalescence and persists for weeks or even months after recovery from the infection. There was no sign of an insufficient functioning of the liver. "It is possible," they say, "that recurrences of this transient disturbance of glucose balance creates a true diabetes more frequently than hitherto believed."

As an explanation for the hyperglycemia during infection, five possibilities present themselves: (1) reduced insulin output; (2) inability of the liver and the muscles to store glycogen readily; (3) the action of insulin may be interfered with as it is in acidosis and fevers; (4) the nervous control mechanism may not be functioning properly; and (5) there may be an increased output of adrenalin which increases the hyperglycemia. Goetzky [17] and Czerny think that the second factor is of prime importance. Hahn,[22] Offenbacher [23] and John [24] think number one is the most probable factor. Various authors have expressed the opinion that the third factor is of major significance. All five may be important and at different times the various factors may be involved in various proportions.

Root and Warren [35] state: "The character of the lesions of the islands of Langerhans suggests a toxic origin acting over a long period of time. . . ."

I have always felt that if liver damage were of prime importance hyperglycemia would be encountered more frequently; furthermore, in patients with marked cirrhosis of the liver, there is no hyperglycemia. Warkany [25] studied the level of fasting blood sugar in a three and a half year old child with cirrhosis of the liver. The fasting blood sugars were normal, 60–106. A glucose tolerance test, using 30 gm. of glucose, produced a normal curve.

Were the insulogenic function involved, the hyperglycemia should be in direct proportion to the insulogenic reserve of the individual. Even here one will not get a clear picture as the problem is a complex one for there can be a marked insulogenic derangement of a temporary nature, which, once relieved, will quickly return to good function; and if not relieved and if prolonged it may go on to a frank diabetic state. That this occurs I [24] have shown in previous publications.

In figure 5 are shown the blood sugar changes during and after pneumonia in a child three years old. I have constructed these curves from Kohn and Felshin's [26] figures. Note the marked rise and slow fall of blood sugar during the crisis and the subsequent drop of the curve after the infection has subsided. In the first curve starvation tends to distort the curve toward the diabetic side. In diabetics during an infection the

insulin requirement is greater and we speak of this as inactivation of insulin. There is also an increased adrenalin output during infection. We might well be dealing with a similar problem in regard to the endogenous insulin in such a case of pneumonia. The important thing is that in most cases the decreased glucose tolerance is but temporary, but occasionally it

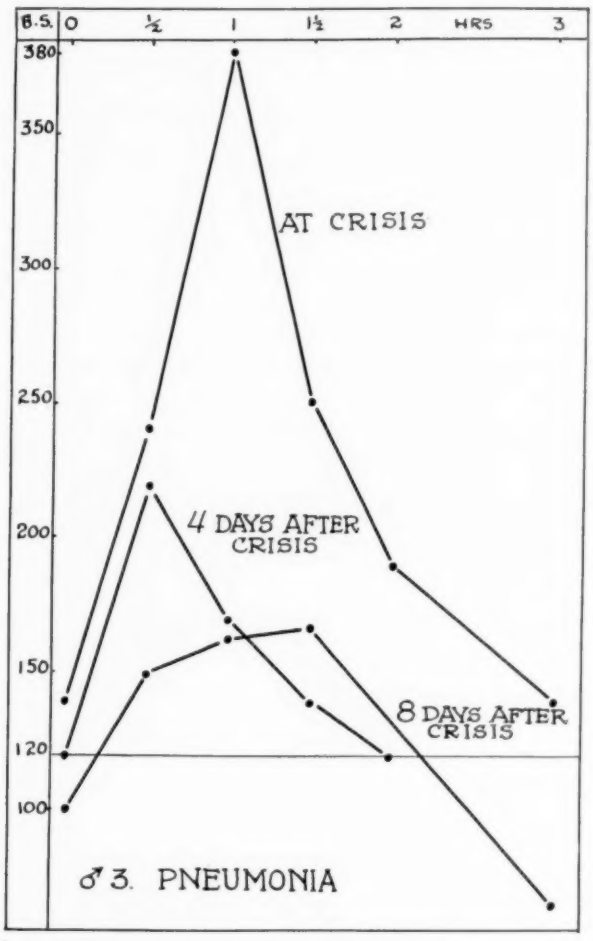

FIG. 5. Glucose tolerance tests in a three year old infant with pneumonia at crisis, four days after crisis and eight days after crisis.

becomes permanent which means that the patient has diabetes. Are these exceptions due to a less efficient insulogenic function with which the child started life? Or is it a certain type of action of bacteria and their toxins on the pancreas? I have no answer to offer.

I have followed out this problem a bit further in a comparative study of glucose tolerance tests on children and adults with various affections.

The findings were quite striking. (Figure 6.) In obesity and hyperthyroidism, for instance, adults show diabetic curves about three times as often as do children. In glycosuria, rheumatism and hypopituitarism the incidence is about the same. In hypopituitary disease there is an increased sugar tolerance. Sixty-six per cent of cases of glycosuria are nondiabetic. Rheumatic conditions and chronic infections carry a heavy

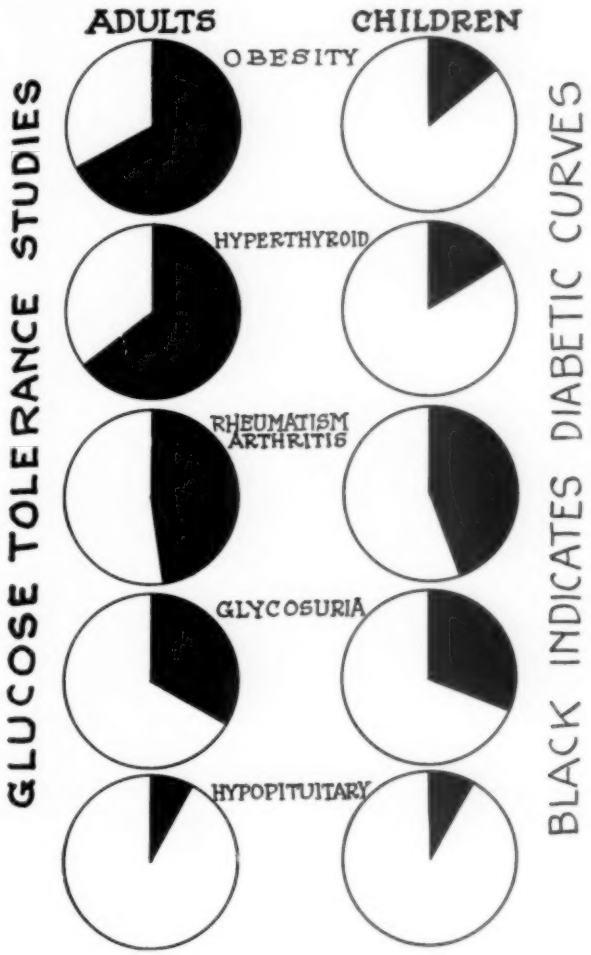

FIG. 6. Comparative studies of glucose tolerance tests in adults and children afflicted with the same condition.

incidence of diabetic curves both in children and adults. Hyperthyroidism does not disturb the carbohydrate tolerance of the child nearly so much as it does that of the adult; the same can be stated regarding obesity. Here then we have the difference, functional I think, between the child and the adult. The child is a better physiological unit on the whole than the adult who has been harassed by infections, wear and tear, dietary abuses et

cetera for decades and has thus exhausted much of his reserve. Any superposed strain on such a background produces a different picture from that where the background is intact.

Obesity

A series of 1306 cases of adiposity was reported in 1925 by Anders and Jameson.[27] In this series the authors found 119 or 9.1 per cent of the patients had diabetes. The general incidence of diabetes is at most 2 per cent so that the increase in the incidence of diabetes as judged from this series is about 500 per cent. In my series of diabetics, 76 per cent of the patients were more than 10 per cent overweight at some time during their lives. The threat of diabetes, then, is very real to the adult who is obese.

The question of obesity in children fortunately does not present such a serious outlook, but Mouriquand [28] in 1920 warned us to be on the alert to detect incipient obesity in children of the obese, the diabetic, the arthritic and the gouty parents. He says that nearly all of his patients who had early inherited obesity developed diabetes before the age of 40; but that when the inherited obesity did not develop until later in life only 50 per cent became diabetic; and in acquired obesity only 15 per cent developed diabetes.

In my glucose tolerance studies on obese children and adults it was shown that the children had three times the resistance to diabetes that the adults had. This is well illustrated in the case reported in 1925 by McKinley [29] of a girl 18 years of age who had endogenous obesity and weighed 346 pounds. Her blood sugar and glucose tolerance test were normal. On the other hand Wagner [30] reported the case of an obese girl, 12 years of age, who was diabetic in the presence of definite hypothyroidism which usually is accompanied by an increased tolerance. Lindblom [31] reports a boy, 16 years old, with hypothyroidism and severe diabetes who died in coma.

However, on the whole, the problem of obesity in children plays but a minor rôle as can be gleaned from figure 7, which shows the incidence of obesity in the various decades in a series of 528 of my cases which I analyzed some time previously. In the first decade it amounts to but 1 per cent, though the second decade already shows an increase.

Nevertheless, one should look upon an obese child with suspicion and settle the problem regarding its carbohydrate metabolism. The treatment of obesity in children depends upon the underlying cause for it, which often is of endocrine origin.

Arteriosclerosis

While arteriosclerosis frequently accompanies diabetes in the older patient and probably plays an important part as an etiologic factor, it is almost a negligible factor in the young. Pearl Zeek,[32] who searched the literature over the last 100 years, found but 98 cases of juvenile arteriosclerosis

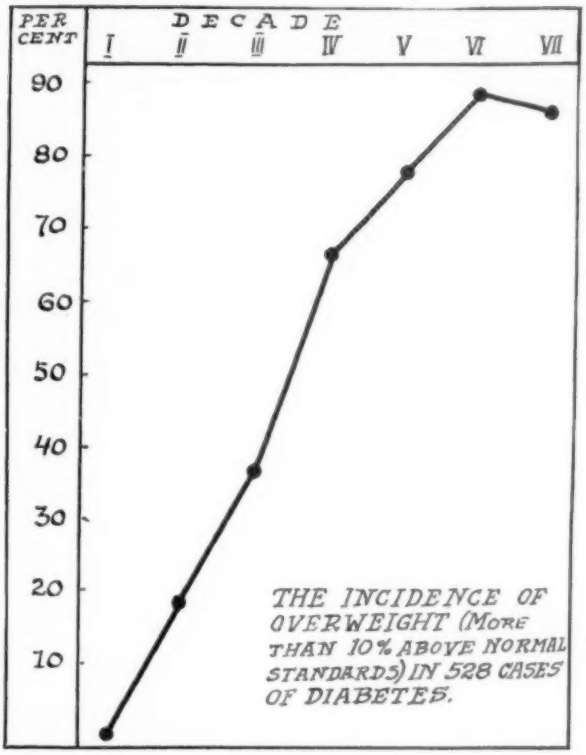

FIG. 7. The incidence of overweight in 528 diabetics from my own series in the various decades.

excluding those due to luetic infections and, as far as could be determined, none had diabetes. Nephritis, lues, and tuberculosis are factors which are most frequently associated with premature arteriosclerosis. Arteriosclerosis, however, does appear in the diabetic child after he has had diabetes for a number of years much more frequently than it does in the nondiabetic child.

HYPERTHYROIDISM

That hyperthyroidism in children is not a rarity is a well known fact. In table 5 I have gathered 285 cases reported in the literature.

In a study of 9,000 hyperthyroid adults [33] I found 6.88 per cent with a derangement of carbohydrate metabolism which manifested itself by a nonphysiological hyperglycemia either with or without glycosuria. This derangement during the acute stage of hyperthyroidism often is considerable. Thus in a series of 239 glucose tolerance tests on adult patients with hyperthyroidism, 64 per cent gave a curve like that of diabetes. I have considered this as a lack of physiological response. Either the glycogen storage function is at fault, or the nervous control mechanism which regulates the insulin output is interfered with, or else there is an abnormal

TABLE V
Toxic Goiter in Children

Author	Year	Number of exophthalmic goiters in children 14 or less	Boys	Girls	Total Exophthalmic Goiters
Helmholz	1921–26	30	4	26	3,432
Sattler	1909	184	39	144	3,477
Lewis	1905–13	5	0	5	1,512
Dinsmore	1926	48	8	40	
White	1912	1 newborn			
Klaus	1914	1 infant 9 mos.			
Klein	1922	3			
Wynter	1911	1			
Pritchard	1910	1			
Woodward	1914	1			
Roilliet	1914	1			
Else-Peden	1925	18			
Lahey		1 (3 yrs.)			
	Total	285			

stimulation of the adrenals producing hyperglycemia, or a temporarily lessened insulogenic function, or the insulin does not act properly as is the case during infections. Any one or all of these factors are possibly of importance but which one predominates and to what extent we do not know.

In a series of 9,000 cases of hyperthyroidism I analyzed 620 cases of glycosuria carefully. During the derangement of the carbohydrate metabolism these patients were closely watched and received adequate insulin for their protection, but not all of them regained their normal insulogenic function. One hundred and eighty-six patients remained diabetic and receive treatment for diabetes to this date. Thus the actual incidence of diabetes in hyperthyroidism in my series was 2.1 per cent with protection. What it would have been without such protection I do not know, but I venture to say that it would have been considerably higher. But even so it is about 100 per cent more than the general incidence of diabetes.

When we come to study the problem of hyperthyroidism in the child we see a different picture. Figure 6 shows that diabetic curves occur in cases of juvenile hyperthyroidism only about one-fourth as frequently as they do in the hyperthyroidism in adults. Apparently the greater reserve or flexibility in the young can withstand a grave metabolic derangement and still right itself. In my own series of children with hyperthyroidism who were protected during and after the acute stage of hyperthyroidism none developed a frank and lasting diabetes. This is in sharp contrast with the adult group. I have under my care, however, two children with diabetes who had some derangement of their carbohydrate metabolism during the acute stage of hyperthyroidism. Both were subjected to thyroidectomy. Both were told by the surgeon to forget about their blood sugar and both returned later with frank diabetes and are under treatment

to this date. Had these children been protected for six months or a year, they might not be diabetic today.

On the whole, hyperthyroidism plays but an insignificant part as an etiologic factor in the production of diabetes in children. When abnormalities in the carbohydrate metabolism are found, they should be controlled thoroughly by a liberal diet and a sufficient amount of insulin to insure proper utilization of the food. Sugar free urine together with normal blood sugar should be attained and maintained long after operation until a complete restoration of function has taken place. Only thus can diabetes from this source be prevented.

Lues

All authors are agreed that luetic infections are of no significance as an etiologic factor in diabetes. Joslin and the European authors express themselves alike in this respect and in my own series I found none in whom syphilis could have been a predisposing factor. Lasalle [34] studied a group of four diabetic infants from poor families and he stated that syphilis was a probable cause of the diabetic condition. While lues does play a small part in the production of diabetes in adults or at least accompanies it, in children it is a negligible factor.

Summary

1. The average percentage of cases of diabetes in children in which heredity was an etiologic factor in a series of 1,413 cases from the literature was 30.8 per cent. In my series of 214 cases of diabetes in children the hereditary incidence was 18.7 per cent. In Jewish children there was a hereditary influence in 39 per cent as contrasted with 19.4 per cent in Gentile children. In my own series, the incidence in Jewish children was 30 per cent and 17.9 per cent in the Gentile group. Diabetes apparently is a recessive character according to the hereditary laws of Mendel. Heredity in 19 pairs of twins is analyzed according to the time interval between the onset of diabetes in each pair. In three pairs it was simultaneous.

2. Infection in diabetic children requires close and adequate management if the child is to emerge from it without further impairment of sugar tolerance. In my own series of diabetic children, in nine cases, or 4.2 per cent, the onset of diabetes followed within 10 days after the infection; in six cases, or 2.8 per cent, the onset was within 20 days; in 45 cases, or 21 per cent, the onset was within 60 days. The onset of diabetes may follow any acute infection and every child should have a weekly urine examination until there is ample evidence that sugar is being utilized normally. In the early stages of diabetes, the process is to a certain extent still a reversible one whereas at a later stage no repair is possible.

3. Comparative studies of glucose tolerance tests in children and in adults having various affections present a striking and an interesting con-

trast between the two groups in obesity and hyperthyroidism. In rheumatism and glycosuria and hypopituitarism they are practically alike.

4. Obesity in the adult presents a high incidence of diabetes, as much as five times the general incidence of the disease. Obesity in children does not present a major etiologic problem.

5. Arteriosclerosis is not a causative factor of juvenile diabetes.

6. Hyperthyroidism plays an insignificant rôle as a causative factor in diabetes in children as contrasted with the same condition in adults. However, nonphysiological hyperglycemia during active hyperthyroidism should not be disregarded and the child should be given protection during this period until the carbohydrate metabolism has returned to its normal function.

7. Lues can be disregarded as a causative factor of diabetes in children.

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PSYCHOLOGICAL CONSIDERATIONS IN THE TREATMENT OF THE NEUROSES*

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THERE can be little question but that a very large proportion of those who consult their physicians for other than purely surgical, acute infectious or obstetrical conditions are suffering from some form of neurosis, which, in many cases, is psychogenic in origin. The *function* of some organ or organs is at fault while the organ itself is in no way diseased. The diagnosis of such a condition as some form of organic disease is one of the commonest errors in diagnosis met with today. The battle-scarred abdominal wall of one who has submitted to one surgical procedure after another in seeking a cure is altogether too commonly seen; nor is it surprising that this should be the case. Ever since the beginnings of scientific medicine in the seventeenth century, and particularly during the last hundred years, the main emphasis in medical education and practice has been on the physical side of man and but little attention has been given to the mental. Most of those who are now practicing medicine were well trained in anatomy, physiology, biological chemistry, pathology and bacteriology but comparatively few received any instruction to speak of in psychology. In the clinical field, too, almost the entire emphasis up until a few years ago was placed on organic disease, and many medical schools have offered courses in clinical psychiatry for the first time during the past half a dozen years. What wonder, therefore, that physicians so largely seek to find a physical basis for all disease states and fail to consider a possible disorder of the psyche. Sir William Osler counseled us always to bear syphilis in mind when making a diagnosis but it is even more true of a neurosis that it can masquerade in the guise of almost any organic disease. To mistake a neurosis for organic disease has the most serious consequences for the patient, as the major surgical or prolonged medical treatment of a neurotic is much more harmful in its consequences for him than for the emotionally stable individual. To differentiate between a functional and an organic condition is often a major test of the diagnostic acumen of the physician.

But when the diagnosis of a neurosis has been made, how should the individual be treated? Plato said, "As you ought not to attempt to cure the eyes without the head or the head without the body, so neither ought you to attempt to cure the body without the mind: and this is the reason why the cure of many diseases is unknown to the physicians of Hellas, because they are ignorant of the whole, which ought to be studied also." The individual must be studied as a whole, both body and mind, in order to determine

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the genesis of his neurotic symptoms. A careful search must be made to find out what, if any, organic disease is present, but the patient's personality must be studied also.

Often a very superficial knowledge of the patient is sufficient, and simple suggestions for rest, a change of scene, slight dietary modifications and sedatives may work wonders. But in other cases, much deeper studies of the patient may be necessary. Herbert Spencer said, "Life is a series of internal adjustments to external environment" and the neurotic person is often one who fails to make the adjustments satisfactorily with resultant deep emotional disturbances which are hard to discover. The emotions are the source of a large part of man's psychic energy when his emotional life runs smoothly. But when it fails to do this and major emotional conflicts develop, the individual is apt to suffer from a neurosis. It may, therefore, be of the utmost importance to understand the emotional make-up of a patient and the way in which he reacts to his particular problems of life. This may entail a detailed survey of the patient's early education and environment, his likes and dislikes, his hopes and fears, his degree of introversion and extroversion, his sexual adjustment and other emotional reactions. One is apt to hear the remark "O! He's just a neurotic" as if a neurotic were an inferior being. This is often far from being the case and the patient is simply emotionally immature rather than inherently inferior. To discover the deep lying emotional factors in a case and then to re-educate the individual to meet his particular problems in life without the development of neurotic symptoms is both the problem and the method of successful approach for the physician. A broad understanding of human nature and some knowledge of so-called "mental mechanisms" is of the greatest help to the physician in accomplishing these aims.

The following cases are reported to show: (1) how a neurosis may simulate organic disease; (2) that the causes of neuroses are often psychological; and (3) that the symptoms usually disappear if the patient's emotional conflicts can be solved. None of these patients had any organic disease which was in any way related to their neurotic disorder.

Case I

The patient complained of intense nervousness and hoarseness. He was in a highly agitated state, could eat and sleep but little and spoke in a hoarse whisper. He had been sued for misuse of funds that had been entrusted to his care and, when called to the stand to testify in his defense, he suddenly lost his voice. The judge granted a postponement so that he could recover his voice and not have to testify under a disadvantage. The man had been receiving local treatments for his aphonia without any benefit and had finally been told that he must stand trial in spite of his physical condition. He felt confident that he could vindicate himself, and his lawyer assured him that he had nothing to worry about. But there were many things about this man's personal life which no one knew about except his opponent and he was afraid that they would come out at his trial. He was no physical coward. Powerfully built, mentally alert he had stroked his university crew and had seen four years of active service at the front during the World War as a captain in the British army. He

had been decorated more than once for bravery under fire but he could not face the possibility of losing his case in court and, with it, his reputation as an honest and highly moral man. He was told that he would not recover the use of his voice until he went through with his trial. The case was tried. The patient testified and promptly recovered his voice and usual calmness even though he was convicted.

This is a typical case of hysterical aphonia which failed to respond to local medical treatment and disappeared only when the emotional conflict which produced it was resolved. Like many of the cases of "shell shock" in the World War, the patient unconsciously developed a symptom which protected him from facing a situation of which he was afraid.

Case II

A white woman of 33 complained of repeated convulsive seizures over a period of nine months and severe backache over a period of 10 years. She had been under various physicians' care at different times for her backache and had received but little help. Finally, 18 months before she came under observation, a suspension was done in the hope that the backache would be cured when her retroverted uterus was put in good position. The objective of the operation was attained but the backache continued. After a slow convalescence of nine months the patient was about to return to her work when she had her first convulsive seizure. Although thorough examinations of many kinds were made, no cause for the convulsions was found and the patient came to the conclusion that she was a hopeless epileptic. In spite of the fact that she had been in the hands of many physicians, none of them had taken the trouble to explore her past life beyond a few perfunctory questions.

An analysis was undertaken. Space will not permit the reporting of the progress of the case in detail but it may be summed up by saying that she had had a frightfully unhappy childhood under the domination of an unusually cruel stepmother and that this had colored her whole subsequent emotional life. As a child the patient, Cinderella-like, had been made to slave in the interests of her younger step-sisters and had been taught to believe that she should always give way for someone else. Starved while her sisters were fed plentifully, the patient stole from the pantry night after night and then cried herself to sleep thinking that she was a wicked girl. At 21 she fell in love and the world looked brighter. Her mind pictured a happy, normal existence: a home, husband, children. But the object of her affection was engaged to another girl whom he did not love. He told the patient that he would break his engagement and marry her. But the second woman was a friend of the patient's and hadn't she been brought up always to sacrifice herself for others more worthy than she? And so, in the end, she gave up the man she loved and refused to marry him. She then determined to forget him and began training to become a trained nurse. She would thus be devoting herself to the service of others who were in need. Then the backaches began. Through the medium of dreams early forgotten memories were recalled. These memories were frequently of unjust and inhuman treatment at the hands of the stepmother. Among other episodes recalled was one in which the stepmother had kicked the patient in the small of the back after a severe scolding for something the patient had not done. The helpless little girl had felt that she would have killed her had she had the means—a wicked thought and one that had to be banished from the mind of a girl with strong religious principles. Another dream dealt with a time when she was stripped and beaten across the back with a whip in the presence of her older brother. Other dreams revealed the fact that the patient was still in love with the man she had refused and whom she thought she had forgotten. And here is another example of the work of an unconscious factor. When

denied normal wifehood and parenthood, the patient had tried to do something she really did not want to do. A neurosis developed which prevented the accomplishment of this substitute existence and a symptom appeared which symbolized the cruelty of the stepmother, the cause of all her trouble, and her hatred for her.

This is another case of hysteria and one which was much more serious in every way than case 1. Even after many conferences, during which a good rapport had been established, ordinary questioning failed to bring out the essential emotional conflict because the patient herself had repressed it. It was only by the use of dream analysis that this conflict was revealed. As the patient gradually recalled early forgotten memories and changed her point of view toward her stepmother and other things, her symptoms disappeared. She is leading a normal, active life today and has not had a convulsion or a pain in the back for over four years.

Case III

A young married woman complained of general "nervousness" and "cystitis." She had all the symptoms of this latter condition in a mild form and had been cystoscoped many times by a very capable urologist, who told her that her bladder appeared normal in every way and that he could find no reason for the frequent return of her symptoms. But although he had seen her off and on for several years, he had never inquired into her sex life beyond a few brief questions such as "is everything all right between you and your husband?"; to which she responded that it was. But, as a matter of fact, it was not. This patient wanted to live, like Peter Pan, in the Never-Never Land of childhood and insisted on continuing to live with her mother after she was married. She hated children and did not want any and she grew up with the belief that all sexuality was "bestial" and "nasty" and resented the fact that she had to have intercourse. Her husband was thoughtful of her feelings and made few demands upon her. And then she discovered that every time they had coitus she developed frequent and painful urination the following day. This necessitated expensive and disagreeable treatments. Wouldn't it be better not to have intercourse so frequently? And so, once more, we find an unconsciously produced symptom helping the patient fight against an undesired adult adjustment.

The treatment of this patient was very unsatisfactory as she refused to believe that her sexual maladjustment and childishness had anything to do with her bladder trouble or general nervousness. Sick and suffering as she was, it was easier for her to live thus than to make the adjustment to her husband and to life in general which her age demanded.

Case IV

A young married woman complained of "heart trouble," which was characterized by fainting spells. These occurred whenever she was under any emotional pressure. She had been the oldest of 10 children and the only girl. Her father was a chronic drunkard and, from a very tender age, the patient had been accustomed to hearing her drunken father making sexual demands on her mother and had lain in bed shivering with fear and disgust as she heard her mother plead with him. She had seen the economic struggle to raise a large family on a small income and had early decided that she would never marry. Then, as time passed, she became conscious of the biological urge to marry and experienced a sexual thrill in company with men. It was at about this time that she began to have fainting spells and she then thought that

she wasn't strong enough to marry and have children, although she greatly desired them. She did marry but with the fixed idea that sexual relationship was only justified in the interest of having children. At the physical consummation of her marriage, she had hysterics and the whole "honeymoon" was a nightmare. For eight years the sexual relationship between her and her husband was entirely unnatural and she would almost always have hysterics—crying, scratching and biting her husband and often ending up with a fainting spell. It was necessary for her to change her attitude toward the whole matter, a painful process for her. But she went at it in good spirit and has not fainted but once in over two years. In addition to this, she also states that she never knew what happiness was before and all her "nervousness" has ceased.

It is certainly far from true to say that all cases of nervousness have a sexual basis but many of them undoubtedly have and it was the underlying factor in this case. From an early age the patient had looked forward to the sexual act with dread and loathing and her sexual life with her husband was most abnormal. Just why her difficulties in this field produced the particular symptoms that she showed would be hard to prove but they all disappeared when her sexual life became normal.

Case V

The patient complained of general "nervousness" and painful menstruation. In giving her history she stated that she had always had some pains with her periods but that they had been particularly severe for the past six years. She had been married about a year before and had submitted to a suspension operation in an attempt to gain relief. This had done no good and the pains had been worse, if anything, since that time. She had also found that the sexual relationship was becoming very distasteful to her and she regretted this as her husband upbraided her for not loving him as she should. His own love for her was very evidently beginning to cool. Inquiry revealed that she had been greatly tempted sexually about six years before and had several times permitted certain friends to take liberties with her that her ethical ideals condemned. She had had a terribly guilty feeling even during the period when she was permitting these intimacies and had often thought of suicide. When she married she wanted to tell her husband of her "sins" but he would not let her and she felt that she was deceiving him as to her morality. The whole subject was frankly discussed but nothing was suggested as to the effect this clearing up of a sore spot might have on her dysmenorrhea. After her next period she said, "You know, its a funny thing but I had scarcely any pain for the first time in years." Other periods have passed and she has been almost entirely free from the severe pains that crippled her. Not only this, but she has experienced a complete change in her enjoyment of the sexual act. Naturally enough her husband has again taken interest in her and has ceased to question her love for him. No suggestion was made as to the possible relationship between the guilt feelings of six years and her menstrual and marital difficulties but the confession of those feelings and a sympathetic discussion of them has apparently cured both the troubles of the mind and body whereas surgical interference accomplished neither.

This case is of particular interest because it shows that such a common complaint as dysmenorrhea may at times be due to an emotional conflict. These conflicts so frequently have to do with sexual matters that the physician is neglecting his duty if he fails to inquire into them. This patient, like so many others, had never been asked anything about her sex life beyond a few perfunctory questions. Physicians hesitate to ask ques-

tions dealing with the sex life of their women patients and yet most women will talk about this subject very freely if their confidence is won and if they understand that this subject may have a very important bearing on their complaint.

Case VI

A married white woman of 27 presented a picture of complete nervous collapse. For four years she had gradually been getting worse until, at the time she was first seen, she was hardly able to lift her head from the pillow or take food. She had lost many pounds in weight because of her severe indigestion, she had lost all interest in things and people, including her husband and son, and was intensely irritable and on the verge of tears. She had received no help from the many physicians to whom she had gone. Most of them had told her that she was "just nervous" but one of them had gone so far as to remove her appendix, which proved to be normal in every way. It was soon established that she and her husband had been practicing coitus interruptus for many years and that she was absolutely frigid while he was very passionate. And yet these matters had never been inquired into by any of the medical consultants and the patient and her husband had not liked to ask how to prevent conception in any other way. The patient was a very immature young woman emotionally who had always been spoiled by a doting mother. She had many peculiar and childish ways of looking at the world, from the difficulties of which she had always shrunk. She and her husband were polar opposites in psychological type and could not understand each other's way of doing things. One's way of doing and looking at things seemed unreasonable to the other. Thus, in spite of a very real affection between them, there were constant misunderstandings which caused friction and unhappiness. Both the patient and her husband felt that they were drifting toward a separation in a perfectly senseless way and yet they felt powerless to help themselves. A psychological reëducation of the patient was undertaken. Gradually a more normal sexual life was established, a more mature way of looking at the problems of her life was developed and the patient and her husband reached a better understanding of each other. With these changes came a return of strength and health, interest in life and love for her husband and child. The patient now has a second child and is leading an unusually active existence.

This patient presented a typical symptom-complex of neurasthenia. She was typical of that class of patients of whom Sir James Paget said, "The patient says she cannot. Her friends say she will not. The truth is, she cannot will." Weak and sick in body, she was spiritually unhappy and her marriage was drifting rapidly upon the rocks. In handling such cases, the physician must strive not only to bring back physical health but he must also teach his patient a new way of life.

Summary

In treating functional nervous cases, the physician cannot neglect to study the mind as well as the body. If he does, his patient is apt to drift away into the hands of a quack, who uses strong suggestive therapy and thus cures him temporarily. Psychotherapy must be used as well as other kinds of therapeutics in order to attain that for which the ancients strove—*mens sana in corpore sano*. This is a necessary goal for the neurotic, for a sick mind is almost certain, sooner or later, to produce a sick body.

THE MEDICAL ASPECTS OF NATIONAL HEALTH INSURANCE *

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NATIONAL Health Insurance is a very live topic today. What is more, it is a very serious thing for the medical profession at large, if not for the public. It is well that we should understand it properly, that we should have some conception of the forms it may take, and it is further important that we, as medical men, should be prepared to advise our governments and communities as to the manner in which it should be conducted—should it eventually come to pass as a government measure or as a service to the community.

It has often been said that medicine is a science and an art. Not often enough, however, has it been pointed out that medicine is a service. Osler has expressed it well. "Medicine," he said, "arose out of the primal sympathy of man with man, out of the desire to help those in sorrow, need and sickness."

Is it not reasonable then that service should be stressed as the outstanding feature of medical practice?

Medicine is not an isolated science; it is rather an assemblage from all the sciences which contribute to an understanding of health and disease in the human being. The application of medical science during recent years has been one of the worthwhile achievements in that it has minimized human suffering, increased the average span of healthy years, and thus added materially to the sum total of man's efficiency, effectiveness and happiness.

Medicine will always be conservative; this is to be expected for it is usually influenced, if not controlled, by those who have passed that period of life which welcomes change; the leaders are experienced and know the sobering effects of personal responsibility for human life.

Change is much more gradual than it appears to be in retrospect. Sydenham (1624–1689) is known as "The English Hippocrates." This one man marks for us the break from Galen's dogmatism, which had enslaved medicine for fifteen centuries, to a philosophical consideration of disease, and his era witnessed a return to the Hippocratic method, the study of the individual patient. Sydenham marks the change, but Sydenham was, after all, only the product of his time, not the instigator of the movement. As you will recall, Boerhaave (1668–1738), at the same period, played a similar rôle in Holland.

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On this continent, the practice of medicine, while perhaps apparently unchanged, has nevertheless undergone a very marked alteration in its method. Today, organized medical services, of one kind or another, have become established on a very extensive scale: so much so, indeed, that much discussion has evolved as to whether or not, in the near future, the new world will emulate those older countries abroad which are now providing, under one name or another, organized medical services.

Sickness is not a personal matter in the sense that its effects are limited to the patient. A communicable disease is spread from the sick to the well. Sickness means loss of income to the patient and decreased production to the community. The vicious circle of disease, poverty and dependence is only too familiar. Obviously, sickness is a national social problem, the cost of which we pay, either directly or indirectly, in every instance.

Glance, if you will, at the vital statistics of this or any other community, and you will find that a large percentage of the deaths which occur may be classified as preventable, and why? This condition of affairs exists because of a universal failure to bring together medical knowledge and medical practice. The most urgent problem in medicine today is not the accumulation of further knowledge, desirable as that undoubtedly is, but to bridge the gap which now exists between knowledge and practice.

This gap is not a new chasm caused by the upheavals of an economic depression. It existed even in our years of prosperity, and it has merely been widened by the depression.

Today, more than ever before, we are concerned with medicine as a service, as one of the social resources of mankind to be used for the benefit of all the human family. In other words, conditions must be so changed as to make the full benefits of curative and preventive medicine available to each and every individual. How is this to be achieved? What are we going to do about it?

A number of explanations may be offered to account for the present undesirable arrangements whereby so many are left without the medical care they need. I believe that the real explanation is to be found in the fact that there is no effort made, under our present system, to overcome the economic barrier which now keeps patient and doctor apart.

The problems arising out of the costs of medical care are usually presented from the point of view of the public, as consumers. We are told that, because sickness is not evenly distributed over the population, in consequence, the costs of sickness are not evenly distributed. We are reminded that, as sickness is unpredictable as to its time of occurrence, severity and cost, it cannot be budgeted for. Furthermore, it is pointed out that wage-earners, who make up the bulk of the population, have, as a rule, no financial resources beyond their weekly earnings. The situation, too, is further complicated by the fact that sickness is most prevalent in the lower income groups. All told, this creates an impossible situation, with the heaviest burden resting on those who are least able to bear it.

There is, of course, a practitioners' point of view to this question of costs of sickness. If the public are unable to pay, the doctor cannot collect the fees he has earned. The sliding scale of fees is used to adjust the fee, according to the medical attendant's judgment, to the ability of the individual or family to pay. Why should a medical practitioner, on this basis, charge his full fee to a thrifty family who, because of their thrift, are able to pay, and reduce his fee to a careless family who, because they are spendthrifts, are unable to pay? This rather obviously gives an unfair advantage to the prodigal and penalizes the thrifty.

If the sliding scale is to be effective, the physician must be capable of assessing ability to pay. It is also presumed that each medical practitioner will have an equal share of practice among all economic groups in order to even out his fees. Unfortunately, the larger the practice among the poor, the less time or opportunity is there to build up a clientele of well-to-do patients. In any case, it is an unsound economic system to overcharge one individual to compensate for the loss incurred through others, who pay less than the cost of service.

The situation from the point of view of the medical profession is made difficult too because our present system fails in not making adequate use of the recently-qualified medical practitioner. The result is that the whole of the individual doctor's life earnings must be made in a comparatively few years.

Nor is this all, for it has come to be expected that the medical profession will assume the obligation of the State in providing indigents with one of the necessities of life, medical care. Surely it is unsound and unfair that one group, the medical profession, should be made to assume a burden which should be borne by the whole community.

The medical profession are proud of their record of gratuitous service to those who are in need. The members of the profession, in general, are always willing to give a certain amount of free service. Such free service, however, should be entirely voluntary, as is given whenever a doctor provides care beyond that for which the patient can pay.

The problem which faces the public and the medical profession may be briefly stated to be the provision of adequate medical care for all, with reasonable remuneration for those providing the medical care, by making it possible for all to contribute their share of the cost.

National Health Insurance is suggested as one means whereby this problem may be solved. The principle of health insurance is, in a word, to shift the economic burden from the individual to the group. The insured pay a premium to a fund out of which the costs of medical care are met.

I should like to deal with two special features, because a lack of understanding of these distorts the whole consideration of national health insurance.

First and foremost is the fact that the public desire a high standard of

medical services and, at the same time, approve of a reasonable remuneration to the doctor for that service. The public realize, too, that it is they who would suffer most from any lowering of standards. The medical profession, on their part, are anxious to provide medical service of a high standard, and, in return, are entitled to expect a reasonable remuneration.

Secondly, the public evince no desire to interfere with the professional side of medical practice; they are willing to meet the desire of the profession to retain full control in this matter.

There is no public dissatisfaction with the medical profession; indeed, we find the very reverse. The public show an appreciation of medicine and a desire to profit more fully of what medicine has to offer. Public dissatisfaction is concerned with the system of medical practice whereby the benefits of medicine are not available to all.

If we start with an appreciation of these truths, we can then view the medical aspects of national health insurance without the bitterness and lack of understanding which arise if it is presumed that the public and the medical profession are at loggerheads over such basic principles of any system of organized medical services.

The medical aspects of national health insurance cannot be entirely divorced from other matters, such, for example, as organization, because of the relationship between organization, costs, et cetera, and the medical services that are to be provided.

The members of the medical profession unfortunately are apt to be extremely individualistic in outlook. The individual practitioner frequently builds up a rather quaint conceit, based upon the adulation of his patients, displaying a complacency that is amusing but revealing, and, above all, an irritation that anyone who has not successfully passed through the fires of medical training should dare to voice an opinion on the subject of medical care.

The medical profession, after all, hold a strategic position in national health insurance because they have a monopoly of the knowledge concerning the main field of service which it is the aim of health insurance to provide. But just as physicians in public health have learned that their group is but one of several contributing to public health services, so must the practitioner of curative medicine come to realize that medical practitioners form but one of several groups taking care of the sick.

If it is desirable, and I believe that it is, that the organized medical profession control the professional side of the medical services in national health insurance, it is just as logical that, in matters of business arrangements for national health insurance, the lay power be supreme.

The relationship is comparable to that which exists in our hospitals between the Board of Governors, a lay body, and the Medical Board, a professional body. This relationship, despite certain difficulties, works very well, and there is no better system to suggest unless a dictatorship is preferable.

While I hold no special brief for national health insurance, yet, up to the present time, it would seem to be the one method of spreading the costs of medical care which has already been used extensively on a national basis. A number of countries have tried health insurance, and while they make many criticisms of it, not one has given it up, and most have extended its scope. A fair conclusion is that they have, at all events, found health insurance to be preferable to the conditions which existed previously.

The organized medical profession have the right to expect that they will be consulted by any government considering health insurance or other legislation affecting the provision of medical care.

Obviously, there is nothing to be gained by a government's consulting a medical profession whose members have no suggestion to make and no opinion to offer beyond the expression of a pious hope that all will be well if things are left to take care of themselves.

Medical practitioners are given few opportunities to use their skill in keeping people well. It seems unlikely that any large percentage of the population will, as individuals, pay fees for health supervision. The payment of medical fees will always be more or less irritating, because we prefer to use our money to buy something we really want.

There has been a considerable amount of annoyance shown by the medical profession over the invasion, by public health services, of what the profession have considered to be the field of private practice. It is only fair to note, however, that the encroachments which have been resented have usually been into fields left unoccupied until the way was opened by the public health services.

A fair criticism of national health insurance is that it has not been preventive either in outlook or in practice. Health supervision on an individual basis is certainly more desirable and should be more effective than a health clinic service.

National health insurance should signify more than lip service to the desirability of prevention; it should mean the systematic practice of preventive medicine by the medical profession. The health insurance practitioner would be paid for his preventive work, and the economic barrier raised by direct fees would be removed from the path of the patient who wishes health supervision in his doctor's office.

It is impossible to provide an adequate medical service without a properly organized health department. It would be possible, with national health insurance, to define the two fields of public health and private practice. No gaps between them need exist. There need be no duplication, and most of the sources of irritation as between the public health services and the practitioners of medicine would be removed. The allotment of health supervision and active immunization to the general practitioner is both desirable and practical, provided the service is paid for.

There are some disease problems which may best be dealt with through clinics of the public health services. Tuberculosis, venereal disease and

mental hygiene require the active participation of the public health nurse, working in and from the clinic, to interpret environmental conditions to the physician and to see that his instructions are carried out in the home. Clinics in these fields are rightly regarded as being essential in the programme for prevention and control.

Mass methods are not applicable to medical care. Neither patient, nor disease, nor treatment can be standardized. Medical care, to be effective, must be rendered on an individual basis.

Experience shows that the best type of medical care is built around the general practitioner. The first objective of national health insurance should be to make available, to all, the services of a general practitioner.

A good deal of sentiment surrounds the title, " family doctor." The centralization which has resulted from modern transportation, along with other forces, has brought to an end the social organization into which the family doctor fitted. The old-time family doctor passed when medicine advanced beyond the acquirement of personal skills.

The general practitioner of today is quite capable of dealing with over 80 per cent of illness. The present tendency of supplanting the general practitioner by a group of specialists, called by the family according to the age of the patient or the part which appears to be diseased, is unsound.

It is the general practitioner who deals best with the individual patient, whether it be as health adviser or to prescribe treatment, because his is the all-round approach that is based upon a general knowledge of his patient's physical, mental and social condition. It is this more intimate general knowledge of his patient which allows the general practitioner to be effective in the psycho-therapy which so many patients require.

Specialism has modified medical practice. Partially or wholly, temporarily or permanently, some branch of modern medicine is restricted to the specialist by reason of his more complete knowledge and skill in a limited field.

Unfortunately the public go to specialists direct because they find more and more medical practitioners refusing to do general practice, with the result that the public have come to regard the general practitioner as being of inferior quality. The public have also observed that hospital staffs are largely made up of specialists, and the public have found the specialist not unwilling to receive patients without any reference from a general practitioner.

To emphasize the rightful place of the general practitioner is not to minimize the need for the medical specialist and consultant. It seems reasonable that a general examination should precede special examinations, and that a correlation of the findings of special examinations should be made from a general rather than from a special point of view.

National health insurance should require that specialists be designated and that they receive their cases through the general practitioner who seeks their assistance in problems of diagnosis or treatment, and, in certain cases,

to provide the therapy indicated. The general practitioner, under such circumstances, takes on many of the functions of the old family doctor, including that of advising his patient as to where competent specialist service, of the kind required, can best be secured.

Much sentimental nonsense has been expressed about freedom of choice of physician. Freedom of choice is desirable because it means the confidence of the patient in the doctor of his choice which is such a valuable element in medical treatment. Free choice means competitive practice which, since it tends to maintain standards of service, is, within limitations, most desirable.

Real freedom of choice of medical attendant is exercised today only by that minority of the population who can have what they want because they have the money to pay for it. Geographic location and economic status limit freedom of choice in a fairly drastic manner for the majority of people. The only freedom of choice, alas, which most of the people now exercise is to decide when they are " sick enough to have a doctor."

National health insurance would make freedom of choice of physician much more of a reality, because every qualified medical practitioner should be eligible to practice, and the economic barrier would be removed. I believe that if the individual relationship between doctor and patient is to be preserved under our social organization, the only way open is to remove the economic barrier of medical fees which now keeps patient and doctor apart.

The need for health insurance grows out of the inability of the individual or family to make economic provision for medical care. The insured group should be limited to those with an income below a figure which makes it unlikely that they can, individually, make provision for illness. It is difficult to set an arbitrary amount, but an income of twenty-five hundred dollars for those with dependants, and twelve hundred dollars for those without dependants, might be considered.

Under our present social organization, there is no reason why the medical profession should be treated differently from the other professions when it is a question of dealing with the well-to-do. For that group, the question of fees should be a matter of personal arrangement between the patient and his medical attendant.

However, there is no reason why those of the well-to-do group should not, if they so desire, insure themselves against hospital costs, which are a major factor in the economic problem of medical care for those above the health insurance income level.

Sickness insurance was originally intended to provide a cash benefit in lieu of wages lost on account of illness. Later, medical care was provided, and now we have arrived at the time when it is advocated that the only benefit which health insurance should provide is adequate medical care for the insured. Adequate medical care means a complete service, at home and in hospital, by doctors, dentists, nurses and auxiliary services.

It is unfortunate that illness of the breadwinner usually means a loss of

income at the very time expenses are increased as a result of the illness. Nevertheless, it is believed that whatever cash allowance is to be provided, to compensate for lost wages, should be paid out of unemployment insurance and not out of health insurance.

The cash benefit has been the cause of most of the difficulties associated with health insurance. It brings in the question of certification, it drains the health insurance fund financially, and, all told, makes administration and finance unduly difficult.

The medical profession are desirous of divorcing health insurance from all benefits other than that of medical care. To do so makes the service clear-cut in its purpose. The medical profession are not particularly concerned as to the " insurance carrier " except in that they would be unalterably opposed to allowing any insurance carrier to come between the doctor and his patient as regards the professional side of the doctor's services.

Public and profession would unite in demanding that national health insurance should place in the hands of the organized medical profession responsibility for the control of the professional side of the medical benefit. In no other way can the public be assured of a high standard of medical care, available as required, leaving the medical profession free to maintain such a service and, at the same time, to discipline its own members. The best results are obtained by giving responsibility to those who provide the service. Individualism can be carried to impractical extremes, and in any organized service, there must be some control and provision to take care of the few recalcitrants found in every group. Beyond that, there would be no change from the present mode of practice. The medical practitioner would have his private patients and would care for his insured clientele as private patients, except that, for their care, he would be paid out of the insurance fund.

The medical care of the indigents is a responsibility of the State. All the arguments advanced in favor of freedom of choice of physician, et cetera, as being essential to the provision of adequate medical care, are equally valid as regards the medical care of the indigent.

Obviously, it would be undesirable to build up two systems of organized medical services, the one for the insured, the other for the indigent. A satisfactory way would be for the State to pay the insurance premiums of the indigent, and thus discharge an obligation, long overdue, to provide the indigent with medical care at the expense of the public as a whole, and to remunerate those who provide the care.

The general principle of payment on the basis of service rendered receives universal support. There does not appear to be any reason for a hard and fast rule as to how health insurance practitioners are to be paid. A certain sum of money will be available for the payment of the practitioners, and there is no good reason why the doctors of each area should not, themselves, decide as to which method they desire to use.

In those areas where there is not a sufficient population to support even

one general practitioner, it appears that some definite salary must be paid to the doctor so as to assure the area of a medical service and the practitioner of a certain income.

In England, the medical profession have selected payment on a capitation basis, which is the payment of a per caput allowance for each insured person.

In some countries, small fees are charged for a permit to secure medical care when illness occurs, or part of the cost of medicines is paid for, direct, by the patient. The purpose of all such fees is to discourage abuse of the service. It is, however, a serious matter to impose any fee, no matter how small, because the object is to remove the barrier of fees and not to discourage the insured from consulting his doctor. Better some abuse than the loss to anyone of the benefit of early diagnosis and treatment.

In conclusion, let it not be forgotten that it is the public—the great consumers—who, ultimately, are going to decide what they are prepared to pay for. This is not the responsibility of the medical profession; they cannot attempt to force upon the public a service for which the public are unable to pay.

Still more important, perhaps, is it to emphasize the fact that it is not the responsibility of the medical profession to furnish a service for which the public are able but unwilling to pay. On the other hand, the medical profession should not deprive the public of medical care for which the public are able and willing to pay through National Health Insurance.

EDITORIAL

UNIVERSITIES AND MEDICAL PATENTS

At the recent meeting of the American Medical Association at Cleveland, Dr. George Blumer introduced a motion, which was passed by the House of Delegates, requesting that a committee be appointed by the Board of Trustees to make a comprehensive study of the situation as to the control of patents covering products and devices used in the practice of medicine.

One of the finer traditions of the medical profession prescribes that the physician shall make freely available to his colleagues and to the public any new medical knowledge which he may have gained, and shall not attempt to restrict the use of this knowledge for purposes of personal advantage.

However, in the last decennium, there has developed on this continent a practice by which the physician patents a medical product or device and then assigns the patent to the university in which he is working, or to some incorporated body allied to the university and created for the purpose of controlling such patents. The university or the allied incorporated body may then market the patent by licensing one or more firms to manufacture and sell the product. Royalties may be paid to the university by such licensees. These royalties may be used to conduct a laboratory in the university to check the character of the product produced by the licensees; they may also be devoted to further research on the product; they may be allotted to general research purposes; and they may be in part expended in payments made to the discoverer or inventor.

This practice is, of course, not confined to the schools of medicine; indeed it is more common in other research departments, as for example in colleges of engineering. The medical patents, however, constitute a special instance since the patenting of medicinal products by medical men appears to violate the traditions of the medical profession. It is no doubt in part for this reason that the American Medical Association is being requested to study the situation. It is also, however, because there are grave doubts in many minds as to whether the very nature of university research will not be altered if financial advantage is to be sought from the outcome of that research.

The purposes for which universities or allied corporations may take out patents are very varied. They may be roughly classed as follows:

(a) Patenting to ensure financial profit to the discoverer or inventor.
(b) Patenting to ensure an income to the university in which the discovery or invention was made.
(c) Patenting to protect the public against inferior products.
(d) Patenting to prevent, by dedication of the patent to the public, any monopoly being established by a commercial agency.

A study of the statements made by universities shows that one or more

of the above purposes are advocated by those whose policy includes the patenting of medical inventions.

Patenting to Ensure Financial Profit to the Discoverer or Inventor. It does not appear that any university has set up machinery for the administration of patents for the sole purpose of procuring financial profit for the discoverer of the method, substance or device which has been patented. However, in several universities or their allied corporations, the policy has been adopted of allotting some share of the profits to the inventor and in some instances no distinction is made in this respect between medical and non-medical inventions. It may be fairly said then that such institutions have adopted a policy which contravenes an old medical tradition.

This tradition that personal profit must not be derived from a medical discovery is adhered to, it must be remembered, not only by the faculties of medical schools but by the far larger number of physicians who are in the practice of medicine outside of these schools. This tradition and that of free service to the poor are potent factors in attracting into the profession men who view their life work as of a higher order than a trade. It would be a sad loss to the world if such men were to be replaced by a type that felt that money was a sufficient recompense, and that for money alone without the ennobling idealism of the finer traditions of the profession, they would be willing to perform the menial and often repugnant personal services that are a part of the physician's task. The men who bear the brunt of these daily demands are those who are also called on to devote much of their time to free work. In a few instances their income is large; on the average it is little more than the salaries of medical research men. This great rank and file of the profession who have lived up to their part of the medical tradition, that of free service, have felt pride in their colleagues in the laboratory who have refused to profit personally by their discoveries. A tendency on the part of these latter to shatter this fine tradition will be a deep hurt to every true physician, a loss of something spiritual that helped him over the sordid parts of his work.

Patenting to Ensure an Income to the University in Which the Discovery or Invention Was Made. The governing bodies of a number of universities have stood by the medical tradition for individuals and have refused to permit their institution to profit from the sale of medical inventions or discoveries. Others apparently feel that such funds are acceptable provided that they be devoted to scientific research.

It is perhaps best not to discuss the ethical questions raised by an institution of learning financing itself by adding to the cost to the public of medical remedies, or to do more than allude to the possible loss of dignity involved when such an institution, which is tax free because it does not operate for profit, manages to secure itself profits from its laboratories by the device of an allied corporation that manages its patent business.

Attention may be drawn, however, to the inequitable distribution of financial rewards that seems certain to occur under any régime of university patents.

It would for example be manifestly unfair if one university were to derive financial profit from work carried on in another institution; and yet just this situation is bound to arise if one institution, which does not patent, publishes its results freely thus enabling another institution, by adding some minor practical adaptation to this work, to take out a patent upon it. It may be predicted that such injustices between institutions will occur until all have adopted the policy of taking out patents or all have foresworn the practice.

Even if, however, all medical schools and institutions were agreed upon a policy of obtaining patent rights upon products discovered or invented in their laboratories it is highly questionable whether in the case of patents on the biologic products the purposes of true equity of return as between various individuals and various schools would be attained under the provisions of the present patent laws. Patents are granted not for the discovery of general laws but for the invention of a device, a method, or a product whereby the principle may be applied. The devising of such a means of application is often of very minor scientific merit as compared with the discovery and proof of the general principle. Yet, were one school to devote its resources in men and material to research on the principle, which is not patentable, the total financial reward might yet go to another institution which made a hasty application of this newly discovered principle, and obtained a patent covering such application.

Our patent laws moreover allow of basic patents which cover not only what is the known method of applying the device or product but all future discoveries in which the basic principle employed is similar. The possible injustices inherent in such basic patents are well illustrated in the instance of the Steenbock patent cited by the British Medical Research Council. This patent, which is owned by the Wisconsin Alumni Research Foundation, covers the process of producing vitamin D in natural substances by irradiation with ultra-violet light. The process was originally applied by Dr. Steenbock to the irradiation of foodstuffs. Later, according to the Medical Research Council, it was discovered in England that the provitamin in these natural substances was ergosterol and that the irradiation of pure ergosterol resulted in a product many thousand times more potent in vitamin D than any previously known. English manufacturers found, however, that the Steenbock patent covered the irradiation of any substance and accordingly to take advantage of an English discovery the English must pay tribute to a corporation allied to the University of Wisconsin.

Those who defend this money making function of universities apparently assume that it will have no deleterious effect upon the character of the scientific work in the universities or upon the prestige of the university in the community. One may be permitted to express grave doubts of the validity of these assumptions.

A scientist who has no plans to earn money for himself or his school by his work usually enjoys discussing his results freely with others. Who doubts but that from such free intercourse valuable new ideas are developed?

How ready will the same man be to suggest to another an idea that has a patentable value which he himself might profit by?

No one doubts but what the prime function of the research departments of a university is to develop science, and not the practical applications of science. There are great laboratories and highly trained men at the command of industry to devote themselves more exclusively to the latter objective. It is apparently assumed, however, that since in the university laboratories the practical applications of science are inevitably studied as a part of more general investigations, the university may profit from these practical results of the work, without affecting the interest of the scientist in the broader aspects of his problems. But one wonders whether the measure of a man's university standing will not be insidiously influenced by considerations of the monetary value of his work. Will it be possible not to recognize his contribution to the university funds by according him more weight in council, a more definite right to advancement, perhaps a larger salary? Will there not be envy and bitterness between departments which have profited through patents by increased facilities, a larger staff, more secretarial help, etc., and those whose subject matter contains nothing patentable? Will not the general direction of research in universities be deflected from the goal of all of the truth for its own sake, to that of the part of the truth that has a possible cash value?

It may prove unwise also to assume that the public esteem of the work of scientists will remain as high when it is known that the scientist or his institution has a financial interest which would be affected by the outcome of his researches. There are no doubt individual scientists whose personal prestige is too great to be influenced even by such circumstances. The majority, however, would find that their statements had been trusted not because it was felt that they more than other men were above personal bias, but only because it had been considered that their university position removed them from any temptation.

It seems very doubtful whether the application of additional income from patents to research possesses advantages to counterbalance the restriction of scientific discussion, the inevitable instances of unjust awards, the increase in the lure of applied science, and the loss of confidence on the part of the public which may be reasonably expected if the policy of procuring funds by patenting medical products is widely adopted by our universities.

Patenting to Protect the Public Against Inferior Products. It is often stated that one of the valuable ends served by university patents on medical products is the protection of the public against the premature general distribution of dangerously potent remedies, and against inferior products. It is admittedly to the advantage of the public that certain drugs and biologic substances should receive extensive clinical trial under adequate control in some of the large university hospitals so that their value and dangers may be learned before they are placed on general sale. To obtain the material for such trials it is necessary that large scale production methods be em-

ployed and the coöperation of manufacturing firms may be essential. These in return may rightfully expect an advantage in the way of an exclusive license for a time to market the product. A patent may, therefore, be necessary to make it possible adequately to test a dangerous remedy. There may at times also be an advantage to the public if the manufacture of an unusually complex drug or remedy is restricted by the license method to those firms which agree to submit their products to the check of an assay in the university laboratories. Such measures may occasionally be necessary but they certainly should be looked upon as of a temporary and emergency nature and not as a proper function of the universities. If there is to be systematic testing of the therapeutic and the toxic properties of drugs and other medicinal agents on the market it should certainly be carried out on all important products by some governmental agency with power to forbid the sale of substandard goods. At least, however, where a university administers a patent in order that adequate testing of the product be made possible, and receives in return only the extra funds it has disbursed, its motives are plainly above criticism.

At present, it may be remarked, certain drug firms are extremely anxious to be licensed to market any drug or foodstuff the patent of which is owned by a university, and they are especially aware of the advantage of being able to state that each lot is assayed in the laboratory of the university. To obtain the advantages of these good advertising points they are quite willing to furnish in royalties the necessary funds for establishing the laboratory in the university and for subsidizing further research which, they must naturally hope, will still further prove the value of the product in question.

There seems to be ground for criticism in this latter feature—the acceptance of royalties to carry on research on a product already on the market. Ordinary men, even scientifically trained, should not be appointed to work on a problem when the publication of unfavorable results might cut short the source of their own salaries, and when they must constantly feel impelled to hang over the laboratory door the old motto "*Honi soit qui mal y pense.*"

Patenting and Dedicating the Patent to the Public. The criticism is frequently offered that if the medical research worker does not patent his invention it will be patented by some one else who may then establish a monopoly and thus make the public pay far more than they would have had to if the patent had been assigned to a university. If a patentable process or method has been published by one man it can only be patented by another if he modifies it fundamentally. However, since this may occur, a number of scientific men in the past have taken the step of securing patents as a matter of record and then throwing them open gratis to public use. This has not always accomplished all that was hoped for since manufacturing firms have been chary of investing the necessary funds for machinery and for advertising when they had no protection against competition. It is questionable, however, whether any really important medical discovery if patented in this way would be allowed to go undeveloped. Drugs and other

medicinal products possessing important new properties rapidly become self advertising and the demand for them is natural and continuous and does not depend on artificial stimulation. In the case then of important medical discoveries it would seem that the university might well encourage the inventor to patent and dedicate his patent to the public. Since the average medical research worker possesses neither the knowledge, the time, nor the means to obtain a patent, a group of alumni might be formed who would undertake this part of the task, feeling that thereby they were not only gaining friends and acclaim for their medical school but also helping to preserve a cherished medical tradition.

We wish well to the Committee of the American Medical Association. Theirs is a difficult and an important task. The medical schools of the country are sharply divided on the point at issue. It is vital in the interests of equity as well as of good feeling that all should be united again. This can be accomplished, we feel, only by the abandonment of the policy of patenting medical inventions for profit.

The right to patent an invention is not a natural right but a privilege granted by the state to reward inventors. The medical profession as a whole have lived by the rule of relinquishing this reward in favor of the public. It would probably meet with the approval of the medical profession if, following the lead of certain other countries, the United States as a measure of public policy removed from the category of patentable articles all products and devices which are to be used by the medical profession with the purpose of curing or preventing disease.

M. C. PINCOFFS

REVIEWS

Recent Advances in Sex and Reproductive Physiology. By J. M. Robson, M.B., B.Sc. (Leeds), F.R.S.E., Beit Memorial Research Fellow, Institute of Animal Genetics, University of Edinburgh. With introduction by Prof. F. A. E. Crew, M.D., D.Sc., F.R.S.E. x + 249 pages; 14 × 21 cm. P. Blakiston's Son and Co., Inc., Philadelphia. 1934. Price, $4.00.

At the very outset it may be said that the present work is a thoroughly sound and acceptable one in every way, and that it may be unreservedly recommended not only to the laboratory investigator, but also to the increasing number of clinicians who are becoming interested in endocrinological problems. The text is introduced by a foreword from Professor F. A. E. Crew, director of the Institute of Animal Genetics at Edinburgh, whose laboratory has been so productive in the field of reproductive physiology.

The author has arranged his subject matter very logically, and it is surprising how thoroughly he has condensed most of the available worthwhile information into such a comparatively small compass. The secret is obviously in the discriminating omission of discussions dealing with relatively unimportant aspects of the general problem. References to the literature are frequent enough, but they are not allowed to mar the readability of the work, as is so often the case. The discussion of the rôles played by the ovarian and pituitary hormones in the cycle, in pregnancy and parturition, and in lactation, as well as the description of the associated cyclical histologic changes, is an excellent epitome of present-day viewpoints. It is perhaps natural that the subject of hormonic control of uterine motility and reactivity, to which the author has made valuable original contributions, has received rather fuller discussion than one might otherwise expect in a work of this size.

There is a short but probably adequate final chapter on Clinical Applications, including a description of the various pregnancy tests. On the whole, however, the chief appeal will probably be to the laboratory investigator wishing to familiarize himself with the present status of research in the field of reproductive physiology, and to the intelligent clinician, particularly the gynecologist and obstetrician, who has the same desire, because of the more intelligent approach to clinical problems which such knowledge makes possible.

E. N.

Allergy in General Practice. By Samuel M. Feinberg, M.D., F.A.C.P. xv + 339 pages; 16 × 24 cm. Lea and Febiger, Philadelphia. 1934. Price, $4.50.

After reading this book one feels that the author has failed in his avowed purpose of enabling "the average physician to attain a simple direct approach to the handling of this group of ailments," and of showing him "how to care for the allergic patient," not because of any inherent faults in the volume itself but because his purpose is practically impossible of attainment. No branch of medicine is subject to so many variables as is allergy. Basically, one is dealing with a myriad of possible etiological agents, specific in nature, and the clinical effect of exposure to these is again subject to many influences as location, concentration, portal of entry, general health of the patient and many other subsidiary factors. As a result, successful study of these cases presents a problem, except in the simplest instances, that demands the guiding hand of broad experience in finding the significant factors among the multitude of confusing possibilities present in almost every case. No moderate sized book, no matter how well written, can ever hope to do more than present clearly the underlying factors involved in allergy, and this the author has undoubtedly achieved in the present volume.

The material in the book is well organized and is clearly presented. The plan of presentation adheres rather closely to the conventional, beginning with a brief but good historical chapter. There then follows a chapter upon anaphylaxis and allergy which rather satisfactorily explains the relationship between the two. One paragraph in this chapter, in which the author states that all manifestations of allergy are to be considered as being essentially the same, with the same causes, the same method of reaching a specific diagnosis and the same specific treatment, is worthy of emphasis.

His discussion of the importance of asthma in chapter three, in which he mentions the economic loss from asthma itself and calls attention to the disability resulting from its complications, is valuable in view of the laissez-faire attitude of some members of the profession toward this condition. The further consideration of the symptomatology, diagnosis and treatment of asthma follows the usual lines and is well presented.

The section on hay fever is well done and the discussion of hay fever pollens by Durham is especially fine.

The last chapter of the book, devoted to "other allergic disorders," is sound but too brief to be of much practical value in handling these cases.

The case reports are very good and should be most helpful to men just beginning this work.

In conclusion, one might say that, whereas the main purpose of the book is only doubtfully achieved, it can be recommended as giving an excellent brief presentation of the subject.

H. M. B.

That Heart of Yours. By S. CALVIN SMITH, M.D., Cardiologist. 212 pages. J. B. Lippincott and Co., Philadelphia. 1934. Price, $2.00.

Dr. Smith has written a number of books on the heart, and in this book he has discussed the heart for the laity. In 10 chapters he describes the normal heart and its troubles. He states: "Although the conquest of heart trouble has been made by Modern Medicine, the conquest of troubled hearts rests largely with the individual."

He emphasizes the importance of the mind in considering heart trouble, and in his first chapter he points out the fact that many heart conditions that give the patient apprehension are primarily emotional. "It cannot be stated too emphatically at the outset of this book that heart protests are not heart disease. . . . Better heart health is attained by easing its load, by lightening its burdens, by the proper interweaving of rest and exercise and by correct daily living."

In his next two chapters he discusses the hazards that the heart usually meets in childhood and adolescence and he emphasizes the fact that "the heart is subjected to unusual demands by the changing physiology of a growing body," and emphasizes the place that diseased tonsils play in heart infection.

In his next chapter he stresses the need for heart hygiene in middle life, and in the next two chapters he discusses "signs that may indicate beginning heart trouble. and the use and abuse of heart rest," and concludes: "When the heart is acutely ill, rest is paramount. As the heart recovers, exercise must be gradually introduced and increased as convalescence advances, if that heart is ever again to become strong and efficient."

In the next two chapters he discusses general suggestions for heart care and in special heart conditions emphasizes the need for temperance in everything, and states: "Act your age."

Throughout this book the author has maintained a very sane position and says nothing that would create fear in the mind of the patient.

In his last chapter on "The Psychology of Reconstruction," he wisely states: "Stop feeling sorry for yourself."

The physician could well add this book to his library to be used as psychotherapy in those all too common cases that continually come to his attention.

J. L. McC.

Modern Drug Encyclopedia and Therapeutic Guide. By JACOB GUTMAN, M.D., Phar.D., F.A.C.P., Consulting Physician, Manhattan General Hospital, New York; formerly Professor of Materia Medica, College of Dentistry, University of the State of New Jersey. xvi + 1393 pages; 17 × 24 cm. Paul B. Hoeber, Inc., New York City. 1934. Price, $7.50.

This encyclopedic compilation of information on drugs is designed to meet the demand of the physician for information concerning the most recent therapeutic agents placed at his command by the laboratories of medical and pharmaceutical research. The volume contains 8,160 modern, non-pharmacopoeial, medicinal preparations, comprising 1,878 drugs and chemicals, 535 biologicals, 860 endocrines, 1,563 ampule medicaments, 209 medical foods, 129 mineral waters, 2,344 individual and group allergens and 642 miscellaneous products.

The arrangement of the individual drugs under the various subdivisions of the book is alphabetical. A monograph, very similar to that used by the United States Pharmacopoeia or New and Nonofficial Remedies has been employed. Information regarding the physical and chemical properties and therapeutic merit is included. Dosage and method of administration form a special feature of each monograph. Besides the name and location of the manufacturer, information is given regarding the sizes in which the product is marketed.

In addition to the pharmaceutic arrangement and descriptive monographs mentioned in the foregoing paragraph, the book contains a therapeutic guide. In this, the drugs and preparations are arranged under headings which indicate their use in general therapeutics.

Many of the substances which have been the subject of research investigation or controversial medical opinion and discussion in medical literature have appended to them an adequate bibliography.

For convenience and rapidity in finding articles a commercial index has been included. In this, manufacturers are listed and under each heading a list of their specialties and products has been compiled.

In the opinion of the reviewer the volume shows evidence of thoroughness and extensive work on the part of the author. In this day of the passing of the nationally known dispensatories and with the prodigious list of new drugs placed on the market each year by enterprising manufacturers, there is definite need for a volume of this kind.

J. C. K., JR.

A Text Book of Pharmacology and Therapeutics. By ARTHUR R. CUSHNY, M.D., LL.D., F.R.S.; 10th Edition Revised by C. W. EDMUNDS, A.B., M.D., and J. A. GUNN, M.A., M.D., D.Sc. 786 pages; 16 × 24 cm. Lea and Febiger, Philadelphia. 1934. Price, $6.50.

This tenth edition of Cushny's classical textbook appears both substantial in physical make-up, and enlarged in the quantity of subject matter. In the present edition changes have been made to conform with the British Pharmacopoeia of 1932. The authors point out also the inclusion of the newer knowledge on liver and stomach preparations in the treatment of primary anemia; the vitamins, iron medication, bismuth in the treatment of syphilis, new hypnotic agents and the recent advances in

the chemistry of digitalis. In this edition the section on the therapeutic uses of the individually considered drugs immediately follows the discussion of their pharmacological action. Another innovation is the inclusion of a short biographical note of the author in place of the usual preface to the first edition, to point out to the future generations that the "Man was greater than the Book."

The authors retain the general method of presentation, i.e. (1) drugs that are not absorbed, (2) drugs that act after absorption. In the opinion of the reviewer, the book might more effectively accomplish its purpose if the drugs were discussed under the heading of the physiological systems upon which they act. It is stimulating to see the newer theories of the action of drugs on cells mentioned in the text. Perhaps the widespread recognition of these theories will tend to bring about a more quantitative concept of drug action. The manner in which the section on narcosis has been brought abreast of the times is worthy of special mention. It is noted that the theory of Bancroft on narcotic action was not included.

Among some of the newer drugs that have been omitted from the text are dinitrophenol, divinyl oxide, trichlorethylene and tribromethanol. In the discussion of insulin it is observed that the work of Biasotti and Houssay on hypophysectomized-depancreatized animals is not included. It is to be regretted that in many instances the chemical formulae included show evidence of lack of careful revision.

In general it may be predicted that the text will continue to occupy the same important place in pharmacology and therapeutics that it has held for the past 35 years.

J. C. K., Jr.

External Diseases of the Eye. By Donald T. Atkinson. 704 pages; 479 illustrations. Lea and Febiger, Philadelphia. 1934. Price, $7.50.

This book of 15 chapters is a welcome addition to the limited number of works which are devoted exclusively to external diseases of the eye. The following list covers the chapter headings of this work:

Chapter I. A Retrospect of Ophthalmology Relating to External Eye Diseases. Chapter II. Diseases of the Eye-Lids. Chapter III. Affections of the Lacrimal Apparatus. Chapter IV. Diseases of the Orbit. Chapter V. Diseases of the Conjunctiva. Chapter VI. Diseases of the Cornea. Chapter VII. Diseases of the Sclera. Chapter VIII. Diseases of the Iris. Chapter IX. Diseases of the Ciliary Body. Chapter X. Glaucoma. Chapter XI. Diseases of the Crystalline Lens. Chapter XII. Diseases of the External Muscles of the Eye. Chapter XIII. Hygiene of the Eyes. Chapter XIV. History Taking and Case Records. Chapter XV. Remedies Used in Treatment of External Diseases of the Eye.

While the author states in his preface that the work is limited to those diseases in which a tentative diagnosis can be made without the ophthalmoscope, it is rather difficult to conceive of diseases of the ciliary body, glaucoma and cataract, as external diseases of the eye. In the chapter on diseases of the eye-lids the author has included material which covers not only those conditions seen in this country, but those seen in some of the tropical countries as well.

The illustrations are reproduced both from clinical cases and also from wax models, and as a rule are most excellent, although a few such as pemphigus of the lids require considerable imagination to be able to recognize anything resembling this condition. In a work containing so many illustrations where the visual appearance is the leading point in diagnosis, it is regrettable that stereopticon pictures were not used so that the reader could get, not only a surface appearance, but also depth values as well. Upon the whole, however, the book is to be recommended for both the specialist and the general practitioner.

C. A. C.

COLLEGE NEWS NOTES

Acknowledgment is made of the following gifts to the College Library of publications by members:

Dr. M. B. Marcellus (Fellow), Palo Alto, Calif.—1 reprint;
Dr. W. R. Riley (Fellow), Battle Creek, Mich.—3 reprints;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—1 reprint;
Dr. Cullen Ward Irish (Associate), Los Angeles, Calif.—1 reprint.

Dr. Jonathan C. Meakins (Fellow and President), Montreal, Canada, was elected President-Elect of the Canadian Medical Association at its annual meeting in Calgary, Alta., June 18 to 22.

At the Cleveland Session of the American Medical Association, the Section on Gastro-Enterology and Proctology elected the following Fellows to office:

Dr. Ernest H. Gaither, Baltimore, Md.—*Vice-Chairman*
Dr. Henry L. Bockus, Philadelphia, Pa.—*Secretary*
Dr. Albert F. R. Andresen, Brooklyn, N. Y.—*Member, Executive Committee*

The American Board of Gastro-Enterology, recently organized at Cleveland, elected the following officers:

Dr. Albert F. R. Andresen (Fellow), Brooklyn, N. Y.—*President*
Dr. Franklin W. White (Fellow), Boston, Mass.—*Vice-President*
Dr. Ernest H. Gaither (Fellow), Baltimore, Md.—*Secretary*
Dr. Frank Smithies (Master), Chicago, Ill.—*Treasurer*

The following were elected additional members of the Board of Regents:

Dr. George W. Eusterman (Fellow), Rochester, Minn.
Dr. Henry L. Bockus (Fellow), Philadelphia, Pa.
Dr. Sidney K. Simon (Fellow), New Orleans, La.
Dr. Adolph Sachs (Fellow), Omaha, Nebr.

At a meeting of the Board of Directors of the Jewish Hospital, Philadelphia, on June 11, Dr. Mitchell Bernstein (Fellow) was elected Senior Attending Physician, beginning July 1.

Dr. Bernstein was elected President on June 5 of the Alumni Association of the Philadelphia College of Pharmacy and Science, from which institution he graduated in 1909, and where he is a member of the Board of Trustees.

Dr. John Favill (Fellow), Chicago, Ill., has been promoted to the rank of Clinical Professor of Neurology at the Rush Medical College of the University of Chicago.

Dr. James E. Paullin (Fellow), Atlanta, Ga., was made President-Elect of the Medical Association of Georgia at its last annual meeting at Augusta, May 11.

Dr. Allen H. Bunce (Fellow), Atlanta, Ga., was reëlected Secretary.

Dr. Julius H. Hess (Fellow), Chicago, Ill., was elected President of the Chicago Medical Society at its last annual meeting, June 19.

A public reception was tendered by the Des Moines Chamber of Commerce to Dr. Walter L. Bierring (Fellow), on June 22, in recognition of his induction into the Presidency of the American Medical Association.

Dr. William H. Robey (Fellow), Boston, Mass., was reëlected President of the Massachusetts Medical Society, June 5, at its annual meeting in Worcester.

OBITUARIES

JAMES EDWIN HOUGHTON, LIEUTENANT COMMANDER, MEDICAL CORPS, UNITED STATES NAVY

James Edwin Houghton, Lieutenant Commander, Medical Corps, United States Navy, died suddenly at Washington, D. C., on May 3, 1934.

Dr. Houghton was born at Northumberland, Pennsylvania, August 11, 1891. He graduated in 1917 from the Medical School of George Washington University, Washington, D. C., and at once entered the Medical Corps of the Navy. During the war he served with a laboratory unit. Subsequently his service was at sea and in San Domingo and on the Asiatic Station, as well as shore duty in the United States. While serving at the U. S. Naval Hospital at Philadelphia, he was lecturer on tropical medicine at Jefferson Medical College. At the time of his death he was Director of Laboratories at the U. S. Naval Medical School, Washington, D. C., and Professor of Tropical Medicine there. He had been tentatively selected as the representative from the Medical Corps of the Navy to serve at the Gorgas Memorial Institute of Tropical and Preventive Medicine in Panama. He was one of the outstanding bacteriologists of the Navy, as well as a leading expert in tropical medicine. He had published a number of professional papers, and had done important work on infectious mononucleosis. He had done much work on the technic of the Kahn test and was instrumental in having it adopted as the commonly used test of the Navy. Dr. Houghton leaves a wife and two children. He was made a Fellow of the American College of Physicians in 1926. He was a member of Sigma Chi Fraternity.

The loss of so brilliant and promising an officer is deeply deplored by the entire Medical Corps.

ADMIRAL PERCEVAL S. ROSSITER, M.D., F.A.C.P.,
Surgeon General, U. S. Navy.

DR. JOHN PETER ZOHLEN

Dr. John P. Zohlen, aged 48, a resident of Sheboygan, Wisconsin, died on June 2, 1934, of agranulocytosis, after an illness of four days.

Dr. Zohlen was born in Germany on September 5, 1886. In his premedical training he took his degrees, Bachelor of Arts and Master of Arts, at St. Lawrence College, Mt. Calvary, graduating in 1909. He attended St. Louis University School of Medicine for two years. Then he transferred to Marquette University Medical School from which he graduated in 1913. He served an internship at the Milwaukee County Hospital, and became a member of the American College of Physicians in 1930. His specialty was gastro-enterology.

At the time of his death he was President of the Sheboygan County Medical Society, and of the Sheboygan Clinic.

Otho A. Fiedler, M.D., F.A.C.P.,
Sheboygan, Wis.

DR. MORRIS HIRSCH KAHN

Dr. Morris Hirsch Kahn (Fellow), Fieldston, New York, N. Y., died, July 13, at Mount Sinai Hospital, aged 45 years. Dr. Kahn, a heart specialist, retired from practice about three years ago because of a heart ailment. He was born at Shklov, Russia, in 1889, came to the United States in his boyhood and attended Cornell University Medical School from which he graduated in 1909. He received the degree of Master of Arts from his alma mater in 1922. He interned at Mount Sinai Hospital, and had been connected with this institution for many years, successively as house physician, resident physician, chief of the clinic for internal medicine and chief of the cardiac clinic. In 1920, he became cardiologist of the Beth Israel Hospital which appointment he held until the time of his retirement.

Dr. Kahn was a member of the New York Academy of Medicine, Society for Experimental Biology and Medicine, New York County Medical Society, Eastern Medical Society, New York State Medical Society and the American Medical Association. He was elected a Fellow of the American College of Physicians on December 30, 1926.

He contributed many scientific articles to leading medical journals, including the Annals of Internal Medicine.

Robert A. Cooke, M.D., F.A.C.P.,
Governor for Eastern New York.